

PCT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C. 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year)
04 November 1999 (04.11.99)

International application No.
PCT/GB99/00308

Applicant's or agent's file reference
JEC/BP5748488

International filing date (day/month/year)
29 January 1999 (29.01.99)

Priority date (day/month/year)
29 January 1998 (29.01.98)

Applicant

KEITH, William, Nicol

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

25 August 1999 (25.08.99)



in a notice effecting later election filed with the International Bureau on:

2. The election ☐ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Lazar Joseph Panakal

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

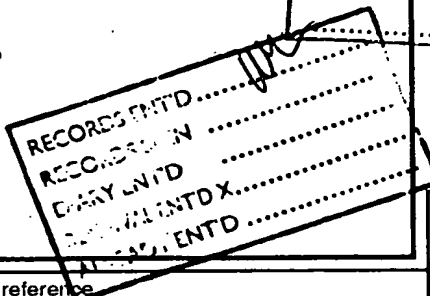
From the INTERNATIONAL SEARCHING AUTHORITY

To:
MEWBURN ELLIS
York House
23 Kingsway
London WC2B 6HP
UNITED KINGDOM

RECEIVED
22 OCT 1999

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)



Date of mailing
(day/month/year) 19/10/1999

Applicant's or agent's file reference

JEC/BP5748488

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.

PCT/GB 99/00308

International filing date
(day/month/year)

29/01/1999

Applicant

CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED et al.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Andria Overbeeke-Siepkens

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/PEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference JEC/BP5748488	FOR FURTHER ACTION <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small>	
International application No. PCT/GB 99/ 00308	International filing date (<i>day/month/year</i>) 29/01/1999	(Earliest) Priority Date (<i>day/month/year</i>) 29/01/1998
Applicant CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.
☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :
- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).
3. ☒ Unity of invention is lacking (see Box II).

4. With regard to the title,

- ☐ the text is approved as submitted by the applicant.
- ☒ the text has been established by this Authority to read as follows:

PROMOTER REGIONS OF THE MOUSE AND HUMAN TELOMERASE RNA COMPONENT GENES

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

- ☐ as suggested by the applicant.
- ☒ because the applicant failed to suggest a figure.
- ☐ because this figure better characterizes the invention.

3a, 3b

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/00308

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 44 and 45 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,
no additional fees are to be refunded.

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☒ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 2-7 (all totally) and claims 1,14,17-18,
37-38 (all partially)

A nucleic acid comprising a promoter region of the human telomerase RNA gene, constructs, vectors and host cells containing it.

2. Claims: 8-13 (all totally) and claims 1,14,17-18,
37-38 (all partially)

A nucleic acid comprising a promoter region of the mouse telomerase RNA gene, constructs, vectors and host cells containing it.

3. Claims: 16 (totally) and claims 15,17-22 (all partially)

A nucleic acid construct comprising a telomerase RNA gene promoter linked to a cytotoxin, and its use in the treatment of cancer.

4. Claims: 23-36 (all totally) and claims 15,
17-22 (all partially)

A method for screening for a substance being a modulator of the promoter of a telomerase RNA gene, the substances identified and their use in the treatment of cancer or the activation of telomerase.

5. Claims: 39-45

A system for controlling neoplasia.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 26, 27 and 32 relate to a substance defined by reference to a desirable characteristic or property, namely its ability to modulate the activity of a TR promoter.

The claims cover all substances having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such substances. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the substance by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the specific modulators as defined in claims 28, 29 and 33.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/00308

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/11 C12N9/12 C12N15/85 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 01835 A (ANDREWS WILLIAM H ;VILLEPONTEAU BRYANT (US); FUNK WALTER (US); FEN) 25 January 1996 (1996-01-25)	1-7,14, 15,17, 18, 23-28, 35,37,38
Y	page 24, line 13 -page 31, line 19 page 37, line 16 -page 43, line 13	15-21, 26-28, 30,31, 35,39-45
A	page 47, line 15 -page 55, line 19 page 65, line 9 -page 66, line 14 --- -/--	26-38

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

5 October 1999

Date of mailing of the international search report

19. 10. 1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Andres, S

INTERNATIONAL SEARCH REPORT

National Application No.

PCT/GB 99/00308

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>PALMITER R D ET AL: "CELL LINEAGE ABLATION IN TRANSGENIC MICE BY CELL-SPECIFIC EXPRESSION OF A TOXIN GENE" CELL, vol. 50, 31 July 1987 (1987-07-31), pages 435-443, XP002055685 ISSN: 0092-8674 the whole document</p>	15-21
Y	<p>FENG J ET AL: "THE RNA COMPONENT OF HUMAN TELOMERASE" SCIENCE, vol. 269, no. 5228, 1 September 1995 (1995-09-01), pages 1236-1241, XP000645335 ISSN: 0036-8075 cited in the application</p>	26-28, 30,31,35
A	<p>the whole document</p>	1-7
Y	<p>RING, C. ET AL.: "Suicide gene expression induced in tumour cells transduced with recombinant adenoviral, retroviral and plasmid vectors containing the ERBB2 promoter" GENE THERAPY., vol. 3, 1996, pages 1094-1103, XP002117436 ISSN: 0969-7128 the whole document</p>	39-45
X	<p>WO 96 01614 A (ANDREWS WILLIAM H ;VILLEPONTEAU BRYANT (US); FUNK WALTER (US); GRE) 25 January 1996 (1996-01-25) cited in the application page 12, line 28 -page 13, line 25 figures 1,3 example 7</p>	1-8,14, 17,18
X	<p>HINKLEY, C. ET AL.: "The mouse telomerase RNA 5'-end lies just upstream of the telomerase template sequence" NUCLEIC ACIDS RESEARCH., vol. 26, 15 January 1998 (1998-01-15), pages 532-536, XP002106807 OXFORD UNIVERSITY PRESS, SURREY., GB ISSN: 0305-1048 the whole document</p>	1-3,8,9, 14,17,18
X	<p>PARKINSON E K ET AL: "The genetic basis of human keratinocyte immortalisation in squamous cell carcinoma development: the role of telomerase reactivation." EUROPEAN JOURNAL OF CANCER, (1997 APR) 33 (5) 727-34, XP002117437</p>	26,31, 32,34, 36-38
A	<p>page 731, paragraph 2 -page 732</p>	26-38
	-/-	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/00308

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>LANDBERG, G. ET AL.: "Telomerase activity is associated with cell cycle deregulation in human breast cancer" CANCER RESEARCH., vol. 57, 1 February 1997 (1997-02-01), pages 549-554, XP002117438 ISSN: 0008-5472</p> <p style="text-align: center;">---</p>	26-38
A	<p>HART L R : "TISSUE- SPECIFIC PROMOTERS IN TARGETING SYSTEMICALLY DELIVERED GENE-THERAPY" SEMINARS IN ONCOLOGY, (FEB 1996) VOL. 23, NO. 1, PP. 154-158., XP002117439 the whole document</p> <p style="text-align: center;">---</p>	39-45
A	<p>WO 95 06486 A (OLDFIELD EDWARD J ;RAM ZVI (US); US HEALTH (US); BLAESE R MICHAEL) 9 March 1995 (1995-03-09) page 14, last paragraph -page 15, line 6 example 1 claims</p> <p style="text-align: center;">---</p>	39-45
A	<p>HARLEY, C. & SHERWOOD, S.: "Telomerase, checkpoints and cancer" CANCER SURVEYS, vol. 29, 1997, pages 263-284, XP002117440</p> <p style="text-align: center;">---</p>	
A	<p>GREIDER C W: "TELOMERE LENGTH REGULATION" ANNUAL REVIEW OF BIOCHEMISTRY, vol. 65, 1996, pages 337-365, XP002056801</p> <p style="text-align: center;">---</p>	
P,X	<p>ZHAO, J.-Q. ET AL.: "Cloning and characterization of human and mouse telomerase RNA gene promoter sequences." ONCOGENE, vol. 16, 1998, pages 1345-1350, XP002106808 ISSN: 0950-9232 the whole document</p> <p style="text-align: center;">---</p>	1-15,17, 18
P,X	<p>WO 98 11207 A (VILLEPONTEAU BRYANT ;HARLEY CALVIN (US); GERON CORP (US)) 19 March 1998 (1998-03-19) page 23, line 25 -page 32, line 13 page 33, line 27 -page 38</p> <p style="text-align: center;">-----</p>	1-7,15, 17-26, 30-32, 34-38

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/00308

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9601835 A	25-01-1996	US 5583016 A	10-12-1996
		US 5776679 A	07-07-1998
		AU 696702 B	17-09-1998
		AU 2964795 A	09-02-1996
		AU 3095095 A	09-02-1996
		AU 9712998 A	18-03-1999
		BG 101103 A	31-10-1997
		BR 9508254 A	23-12-1997
		CA 2194393 A	25-01-1996
		CN 1158617 A	03-09-1997
		CN 1168696 A	24-12-1997
		CZ 9700034 A	15-10-1997
		EP 0778842 A	18-06-1997
		EP 0793719 A	10-09-1997
		FI 970026 A	03-03-1997
		HU 78054 A	28-07-1999
		JP 10505488 T	02-06-1998
		JP 10507067 T	14-07-1998
		NO 970041 A	06-03-1997
		NZ 289720 A	29-03-1999
		PL 318169 A	26-05-1997
		WO 9601614 A	25-01-1998
		US 5876979 A	02-03-1999
		US 5837857 A	17-11-1998
WO 9601614 A	25-01-1996	US 5583016 A	10-12-1996
		US 5876979 A	02-03-1999
		AU 696702 B	17-09-1998
		AU 2964795 A	09-02-1996
		AU 3095095 A	09-02-1996
		AU 9712998 A	18-03-1999
		BG 101103 A	31-10-1997
		BR 9508254 A	23-12-1997
		CA 2194393 A	25-01-1996
		CN 1158617 A	03-09-1997
		CN 1168696 A	24-12-1997
		CZ 9700034 A	15-10-1997
		EP 0778842 A	18-06-1997
		EP 0793719 A	10-09-1997
		FI 970026 A	03-03-1997
		HU 78054 A	28-07-1999
		JP 10505488 T	02-06-1998
		JP 10507067 T	14-07-1998
		NO 970041 A	06-03-1997
		NZ 289720 A	29-03-1999
		PL 318169 A	26-05-1997
		WO 9601835 A	25-01-1996
		US 5776679 A	07-07-1999
		US 5837857 A	17-11-1998
WO 9506486 A	09-03-1995	CA 2169557 A	09-03-1995
		EP 0716614 A	19-06-1996
		JP 9505557 T	03-06-1997
WO 9811207 A	19-03-1998	AU 4351997 A	02-04-1998

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference JEC/BP5748488
(if desired) (12 characters maximum)

Box No. I TITLE OF INVENTION A GENE PROMOTER

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED
Cambridge House
6-10 Cambridge Terrace
Regent's Park
LONDON
NW1 4JL
GB

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State (that is, country) of nationality: GB

State (that is, country) of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

KEITH William Nicol
CRC Department of Medical Oncology
University of Glasgow
CRC Beatson Laboratories
Garscube Estate
Switchback Road
Glasgow
G61 1BD
GB

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (if this check-box is marked, do not fill in below.)

State (that is, country) of nationality: GB

State (that is, country) of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent

☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

JOANNA E CRIPPS and others
MEWBURN ELLIS
YORK HOUSE
23 KINGSWAY
LONDON WC2B 6HP
GB

Telephone No. 0117 9266411

Facsimile No. +44 171 240 9339

Teleprinter No. 22762 PATENT G

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. V

DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

- ☒ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection desired, specify on dotted line):

- | | |
|---|---|
| <input checked="" type="checkbox"/> AL Albania..... | <input checked="" type="checkbox"/> LS Lesotho..... |
| <input checked="" type="checkbox"/> AM Armenia..... | <input checked="" type="checkbox"/> LT Lithuania |
| <input checked="" type="checkbox"/> AT Austria..... | <input checked="" type="checkbox"/> LU Luxembourg |
| <input checked="" type="checkbox"/> AU Australia..... | <input checked="" type="checkbox"/> LV Latvia..... |
| <input checked="" type="checkbox"/> AZ Azerbaijan..... | <input checked="" type="checkbox"/> MD Republic of Moldova |
| <input checked="" type="checkbox"/> BA Bosnia & Herzegovina..... | <input checked="" type="checkbox"/> MG Madagascar |
| <input checked="" type="checkbox"/> BB Barbados..... | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia... |
| <input checked="" type="checkbox"/> BG Bulgaria..... | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> BR Brazil..... | <input checked="" type="checkbox"/> MW Malawi..... |
| <input checked="" type="checkbox"/> BY Belarus..... | <input checked="" type="checkbox"/> MX Mexico..... |
| <input checked="" type="checkbox"/> CA Canada..... | <input checked="" type="checkbox"/> NO Norway |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein..... | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> CN China..... | <input checked="" type="checkbox"/> PL Poland |
| <input checked="" type="checkbox"/> CU Cuba..... | <input checked="" type="checkbox"/> PT Portugal |
| <input checked="" type="checkbox"/> CZ Czech Republic..... | <input checked="" type="checkbox"/> RO Romania |
| <input checked="" type="checkbox"/> DE Germany..... | <input checked="" type="checkbox"/> RU Russian Federation |
| <input checked="" type="checkbox"/> DK Denmark..... | <input checked="" type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> EE Estonia..... | <input checked="" type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> ES Spain..... | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> FI Finland..... | <input checked="" type="checkbox"/> SI Slovenia |
| <input checked="" type="checkbox"/> GB United Kingdom..... | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> GE Georgia..... | <input checked="" type="checkbox"/> SL Sierra Leone..... |
| <input checked="" type="checkbox"/> GH Ghana..... | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> GM Gambia..... | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input checked="" type="checkbox"/> HR Croatia..... | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> IL Israel..... | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> IS Iceland..... | <input checked="" type="checkbox"/> US United States of America..... |
| <input checked="" type="checkbox"/> JP Japan..... | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> KE Kenya..... | <input checked="" type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> KG Kyrgyzstan..... | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea..... | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> KR Republic of Korea..... | |
| <input checked="" type="checkbox"/> KZ Kazakstan | |
| <input checked="" type="checkbox"/> LC St Lucia | |
| <input checked="" type="checkbox"/> LK Sri Lanka | |
| <input checked="" type="checkbox"/> LR Liberia..... | |

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☒ GD Grenada.....
- ☒ IN India
- ☒ Any other state which is party to the PCT

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement.

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.
(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

Supplemental Box*If the Supplemental Box is not used, this sheet need not be included in the request.**Use this box in the following cases:***I. If, in any of the Boxes, the space is insufficient to furnish all the information:***in particular:*

- (i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available:
- (ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked:
- (iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America:
- (iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents:
- (v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "Continuation" or "Continuation-in-part":
- (vi) if in Box No. VI there are more than three earlier applications whose priority is claimed:
- (vii) if, in Box No. VI, the earlier application is an ARIPO application:

*In such case, write "Continuation of Box No. ..." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient;**in such case, write "Continuation of Box III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this box is the applicant's state (that is, country) of residence if no state of residence is indicated below;**in such case write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;**in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;**in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;**in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;**in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.**in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.***2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement:***in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each state so excluded.***3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty:***in such case, write "Statement Concerning Non-Prejudicial Disclosures or Exceptions to Lack of Novelty" and furnish that statement below.***Continuation of Box IV**

ARMITAGE, IAN M.
 BRASNETT, ADRIAN H.
 BREWSTER, ANDREA R.
 CALDERBANK, T. ROGER
 CARTER, STEVEN J.
 COLEIRO, RAYMOND
 CRIPPS, JOANNA E.
 FORD, MICHAEL F.
 GURA, H. ALAN
 HACKNEY, NIGEL J.
 HAMILTON, ALISTAIR
 HARRISON, DAVID C.
 KIDDLE, SIMON J.
 KREMER, SIMON M.
 LINN, S. JONATHAN
 LYONS, JUNE, M.
 NICHOLLS, KATHRYN M.
 O'BRIEN, CAROLINE J.
 PAGET, HUGH C.E.
 SANDERSON, MICHAEL J.
 STONER, G. PATRICK
 STUART, IAN
 WALTON, SEÁN M.
 WATKIN, TIMOTHY L.

Box No. VI		PRIORITY CLAIM		<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box	
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:			
		national application: country	regional application: * regional Office	international application: receiving Office	
item (1) 29 January 1998	9801902.9	GB			
item (2)					
item (3)					
<input checked="" type="checkbox"/> The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): (1) _____					
<small>* Where the earlier application is an ARIPO application, it is mandatory to indicate in the supplemental box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.</small>					
Box No. VII					
INTERNATIONAL SEARCHING AUTHORITY					
Choice of International Searching Authority (ISA) <small>(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):</small> ISA /			Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority): Date (day/month/year) Number Country (or regional Office)		
Box No. VIII					
CHECK LIST; LANGUAGE OF FILING					
This international application contains the following number of sheets: request : 4 description (excluding sequence listing part) : 71 claims : 7 abstract : 1 drawings : 29 sequence listing part of description : 0 Total number of sheets : 112		This international application is accompanied by the item(s) marked below: 1. <input checked="" type="checkbox"/> fee calculation sheet 2. <input checked="" type="checkbox"/> separate signed power of attorney 3. <input checked="" type="checkbox"/> copy of general power of attorney; reference number, if any: 4. <input type="checkbox"/> statement explaining lack of signature 5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): 6. <input type="checkbox"/> translation of international application into (language): 7. <input type="checkbox"/> separate indications concerning deposited microorganisms or other biological material 8. <input type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form 9. <input checked="" type="checkbox"/> other (specify): Form 23/77			
Figure of the drawings which should accompany the abstract 5		Language of filing of the international application: ENGLISH			
Box No. IX					
SIGNATURE OF APPLICANT OR AGENT					
<small>Next to each signature indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).</small>					
..... CRIPPS, JOANNA E. (Appointed Agent) APPOINTED AGENT					

For receiving Office use only	
1. Date of actual receipt of the purported international application: 3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: 4. Date of timely receipt of the required corrections under PCT Article 11(2): 5. International Searching Authority (if two or more are competent): ISA/	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received: 6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid

For International Bureau use only		
Date of receipt of the record copy by the International Bureau:		
Form PCT/RO/101 (last sheet) (July 1998)	MEWBURN ELLIS 21.09.98	See Notes to the request form

PATENT COOPERATION TREATY

in the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

CRIPPS, Joanna E. et al.
Mewburn Ellis
York House
23 Kingsway
London WC2B 6HP
GRANDE BRETAGNE

RECEIVED

25 APR 2000

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing
(day/month/year)

20.04.00

Applicant's or agent's file reference
JEC/BP5748488

IMPORTANT NOTIFICATION

International application No.
PCT/GB99/00308

International filing date (day/month/year)
29/01/1999

Priority date (day/month/year)
29/01/1998

Applicant

CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Vullo, C

Tel. +49 89 2399-8061



PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JEC/BP5748488	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB99/00308	International filing date (day/month/year) 29/01/1999	Priority date (day/month/year) 29/01/1998
International Patent Classification (IPC) or national classification and IPC C12N15/11		
Applicant CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 9 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 25/08/1999	Date of completion of this report 20.04.00
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Moonen, P Telephone No. +49 89 2399 8538 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/00308

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-71 as originally filed

Claims, No.:

1-25 as received on 31/03/2000 with letter of 27/03/2000

Drawings, sheets:

1/29-29/29 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
☐ paid additional fees.
☐ paid additional fees under protest.
☒ neither restricted nor paid additional fees.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/00308

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
- ☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
- ☐ all parts.
- ☒ the parts relating to claims Nos. 2-3 completely; 1,4-5,8-9,17-18 partially.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-3 (completely); 1, 4-5, 8-9, 17-18 (partially)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	2-3 (completely); 1, 4-5, 8-9, 17-18 (partially)
Industrial applicability (IA)	Yes:	Claims	2-3 (completely); 1, 4-5, 8-9, 17-18 (partially)
	No:	Claims	

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/00308

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/00308

Reference is made to the following documents, cited in the Search Report:

- D1: WO 96 01835 (Geron Corp.)
- D2: Nucleic Acids Research **26** (15.01.98) 532-536 (Hinkley et al.)
- D3: WO 96 01614 (CSH LAB et al.)
- D4: Oncogene **16** (1998) 1345-50; P,X-document
- D5: WO 98 11207 (Villeponteau et al.), published 19-03-1998; P,X-document

Introduction

1. The International Search Authority (ISA) identified in the originally filed claims five inventions for the reasons mentioned in the extra sheets attached to Form PCT/ISA/206 sent to the Applicant 14.07.99.

The Applicant decided to pay all the requested 4 additional search fees under protest with an extensive motivation in the reply letter of 13.08.99.

The Review Panel of the International Search Authority confirmed the reasons for the request to either restrict the claimed subject-matter or pay additional fees.

The present International Preliminary Examining Authority issued on 17.12.1999 an invitation to either restrict or pay additional fees. The Applicant's response has been the filing of a new set of claims, still considered not to be unitarily linked and the **first invention** identified in the invitation to restrict or pay is therefore **only** the subject of **further examination** (concerning an isolated promoter region derived of the **human** telomerase RNA (TR) gene promoter, constructs, vectors and host cells containing it): this invention is presently referred to in **claims 2-3** (completely), **and claims 1, 4-5, 8-9, 17-18** (partially, in so far as referring to human sequences only).

Re Item IV

Lack of unity of invention

2. The International Preliminary Examining Authority (IPEA) agreed with the ISA in the identification of the independent inventions in the present application, which

for the present set of claims is as follows:

- i. **Claims 2-3** (completely), **and claims 1, 4-5, 8-9, 17-18** (partially): concerning an isolated promoter sequence derived from the **human** TR gene, constructs, vectors and host cells containing it;
 - ii. **Claims 1, 4-5, 8-9, 17-18** (partially): concerning an isolated promoter sequence derived from **an undefined (eg mouse)** telomerase RNA gene, constructs, vectors and host cells containing it;
 - iii. **Claim 6-7 and 10-13** (completely), **and claims 8-9, 17-18** (partially): concerning a nucleic acid construct of undefined length comprising a telomerase RNA gene promoter sequence operably linked to a heterologous gene cytotoxin, and its use in the treatment of cancer;
 - iv. **Claims 14-16**: concerning a method for screening for a substance being a modulator of the promoter of a telomerase RNA gene, the substances identified and their use in the treatment of cancer or the activation of telomerase;
 - v. **Claims 19-25**: concerning a system to control neoplasia or method of treating neoplasia.
3. With respect to the reasons for the observation of non-unity the following is noted:

A single inventive concept is not provided by the feature of an "isolated promoter sequence (initiating transcription of DNA operably linked downstream) derived from the telomerase RNA gene promoter having approx. 505 bp upstream of the transcription start site or a fragment thereof" (the length of the promoter still undefined by the wording having), in particular on the basis of the disclosure of D2: see e.g. page 534 paragraph with the heading "DNA-sequence analysis of **human and mouse telomerase RNA promoter regions**" and Figure 3. The sequence of the mouse telomerase-RNA gene extends 89 bp upstream of the transcription start site indicated in Figure 3 and contains several identified promoter elements and therefore is considered to be prejudicial to the novelty of the subject-matter of claim 1 (although the transcriptional start site is differently identified).

Even if account is taken from the fact that none of the cited prior art documents comprise a (fully) identified **functional** promoter than it is submitted that the skilled person was in the position to identify the functional promoter sequence on

the basis of the separate disclosures of the human and mouse TR gene sequence: see for the human sequence D1, as well as Figure 1B and 7A of D3 with the transcriptional start site at bp 1459 in Fig.1B; for the mouse sequence see D2, as well as Figure 3 of D3 with the presently identified transcriptional start at bp 606. It is noted that transcriptional start sites for both the human and mouse TR RNA genes had already been established (see e.g. Figure 7A of D3) and assays for detecting promoter activity in the 5'-flanking regions were already known (e.g. a firefly luciferase reporter gene). Thus, between the identification of the full human and mouse TR promoter sequences already present in disclosed sequences flanking the 5'-end of known telomerase RNA-coding sequences there is no new and inventive link. The system of claim 19 based in part to a claim lacking novelty (e.g. claim 1) is not necessarily linked to the inventive concepts of identified inventions I and ii.

A similar reasoning applies to inventions ii and iv: nucleic acid sequences comprising a TR promoter or a fragment thereof were known (see e.g. D3 as mentioned above) and the concepts of inventions ii and iv are neither linked with each other nor with the finding of the isolated sequences of the full functional human and mouse TR promoter.

Therefore, a common, special technical feature referred to in Rule 13 PCT and the PCT Preliminary Examination Guidelines Ch.III, 7 is missing.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

4. The presently examined application refers to the finding of the actual sequence of the human TR gene promoter bases in the complete sequence of the TR gene.

D1-D3 (and D5) are all publications by the same research group or researchers closely working together. D2 is the most recent prior art study for identifying the mouse telomerase RNA 5'-end (just 2 nt from the telomerase-RNA template sequence) and also the 5'-end of the human telomerase 45 nt from the telomerase-RNA template sequence: it does not claim the isolation and identification of the 5'-end flanking region with the functional promoter, only of

related human and mouse telomerase RNA promoter elements in specified regions (page 534 right column), with homology to elements typical of RNA polymerase II mRNA-type promoters. However, the identified TATA and CCAAT boxes (see Figure 3) appear to act as a "minimal promoter"; D2 is considered to be the document providing the skilled person with the teaching for further study of the transcriptional unit flanking the 5'-end comprising e.g. enhancer, CCAAT box, TATA box, Sp1 site etc. (also referred to on page 21 of D1). Furthermore, D1 has referred to the modulation of the transcription of a reporter polynucleotide sequence (e.g. a luciferase gene) operably linked to a transcriptional regulatory sequence (promoter and **upstream** transcription factor binding sites) of a human telomerase RNA component gene in a metabolically active mammalian cell (see paragraph bridging pages 12-13 of D1). Indeed the sequence contains e.g. consensus sequences for e.g. Sp1.

It is therefore considered to have been obvious for the skilled person at the priority date which steps to take in the identification of the transcriptional regulatory sequence, that is the linking of the sequence of the 1459 bases as well as the sequence of about 60 bases containing only the CCAAT and TATA boxes to a reporter polynucleotide sequence in addition to sequences having added bases upstream of said 60 bases in correspondence to the sequence of the 1459 bases. It is submitted that this could be carried out by the skilled person on the basis of the disclosure of D2 in combination with the teaching of D1 to find the essential sequences of the full functional promoter. An inventive step is therefore denied for the subject-matter of all claims of the examined invention (Article 33(3) PCT).

5. None of the present claims of the examined invention is limited by the applied wording to the promoter sequence as present in hProm505, demonstrated in Fig. 5A to be a particularly effective promoter. A claim clearly limited to the promoter sequence of 505 nucleotides in the hTR gene may be considered to involve an inventive step (present claims 1 and 2 are not excluding the presence of additional 5' end sequences of the hTR gene in the isolated promoter sequence by the use of the wording "having" in stead of "consisting": see page 5, last paragraph).

It is noted that it is an error is made in the last paragraph on page 5 as reference

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/00308

is made to position -463 as shown in Fig.4(A); this should be position -436.

Re Item VI

Certain documents cited

Certain published documents (Rule 70.10)

Application No claim)	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid (day/month/year)
WO 98 11207 (D5)	19.03.98	16.09.97	16.09.96

Re Item VIII

Certain observations on the international application

6. In the present report the documents D4-D5 cited in the International Search Report as "P,X-document" have not been considered as the priority document is not available.

M 31.03.00

- 72 -

Claims

1. An isolated promoter sequence derived from the telomerase RNA (TR) gene promoter, having approximately 505 bp upstream of the transcription start site or a
5 fragment thereof, capable of initiating transcription of DNA operably linked downstream of said promoter.
2. An isolated promoter sequence according to claim 1 wherein the promoter sequence is construct hProm505 as
10 shown in Fig 4a and Fig 5a.
3. An isolated promoter sequence according to claim 1 or claim 2 wherein the promoter sequence is 230 bp in length starting at position -42 bp as shown in Fig 4a and
15 Fig 5a upstream of the transcription start site.
4. An isolated promoter sequence according to any one of the preceding claims having the sequence as shown in Fig 4a or mutant, allele, derivative or variant thereof.
20
5. An isolated promoter sequence according to any one of the preceding claims operably linked to a heterologous nucleic acid coding sequence or a gene.
- 25 6. A nucleic acid construct comprising a promoter sequence according to any one of claims 1 to 4, operably linked to a heterologous gene.

AMENDED SHEET

M 31.03.00

- 73 -

7. A nucleic acid construct according to claim 6 wherein the heterologous gene encodes a cytotoxin.
8. A vector comprising an isolated promoter sequence according to any one of claims 1 to 5 or a nucleic acid construct according to claim 6 or claim 7.
9. A host cell comprising an isolated promoter sequence according to any one of claims 1 to 5 or a vector according to claim 8.
10. A host cell comprising a nucleic acid construct according to claim 6 or claim 7.
11. A method comprising culturing a host cell according to claim 10 under conditions for transcription of said heterologous sequence from the promoter.
12. A method according to claim 11 wherein the heterologous sequence is a coding sequence and the host cell is cultured under conditions for expression of the encoded peptide or polypeptide product.
13. A method according to claim 10 or claim 11 comprising detection of transcription of the heterologous sequence or the encoded product.

M 03.00

- 74 -

14. A method of screening for ability of a substance to modulate activity of a TR promoter, the method comprising contacting an expression system containing a nucleic acid construct according to claim 6 with a test or candidate
5 substance and determining transcription of the heterologous sequence or expression of the encoded peptide or polypeptide product.

15. A method according to claim 14 wherein the
10 expression system comprises a host cell containing said nucleic acid construct.

16. A method which comprises, following identification of a substance having the ability to modulate activity of
15 a TR promoter in accordance with a method according to claim 14 or claim 15, manufacture of the substance and/or use of the substance in manufacture or formulation of a composition.

20 17. A vector according to claim 8 for use in a method of gene therapy.

18. Use of a vector according to claim 8 in the preparation of a medicament for the treatment of cancer.

25

19. A system for use in the control of neoplasia in a human or animal subject comprising a vector or other

M 03.03.00

- 75 -

delivery system capable of selectively infecting tumour cells in said subject, said vector carrying a DNA or RNA sequence encoding an enzyme operably linked to a nucleic acid molecule according to any one of claims 1 to 5, in
5 association with a prodrug capable of being converted to an active compound by action of said enzyme.

20. A system according to claim 19 wherein the vector is the gene therapy vector pGT62-codAupp.

10

21. A system according to claim 19 or 20 wherein the enzyme is viral thymidine kinase.

22. A system according to claim 19 or 21 wherein the
15 prodrug is ganciclovir.

23. Use of a system according to any one of claims 19 to 22 in the preparation of a medicament for the treatment of neoplasia in a human or animal subject.

20

24. A method of treating neoplasia in a human or animal subject requiring such treatment comprising administering to the subject an effective amount of a prodrug and a modified virus capable of selectively infecting tumour
25 cells in said subject, said virus carrying a DNA or RNA sequence encoding an enzyme capable of converting said prodrug to an active compound, wherein said DNA or RNA

M 01.03.00

- 76 -

sequence is operably linked to a nucleic acid molecule
according to any one of claim 1 to 5.

25. A method according to claim 24 wherein the enzyme
5 is viral thymidine kinase and the prodrug is ganciclovir.

**REPLACED BY
ART 34 AMDT**Claims

1. A nucleic acid molecule comprising a promoter
sequence derived from the telomerase RNA (TR) gene
promoter.

2. A nucleic acid molecule according to claim 1 wherein
the promoter sequence is derived from the human TR (hTR)
gene promoter.

3. A nucleic acid molecule according to claim 1 or
claim 2 wherein the promoter sequence is derived from a
nucleotide sequence as shown in Fig. 4a.

4. A nucleic acid molecule according to any one of the
preceding claims wherein the promoter sequence is at
least 230bp in length starting at position -42bp as shown
in Fig. 4a and Fig 5a upstream of the transcription start
site.

5. A nucleic acid molecule according to any of the
preceding claims wherein the promoter sequence comprises
the construct hProm505 as shown in Fig.4a and Fig.5a.

6. A nucleic acid molecule according to any one of the
preceding claims wherein the promoter sequence comprises
the construct hProm867 as shown in Fig. 4a and Fig. 5a.

7. A nucleic acid molecule according to any one of the
preceding claims wherein the promoter sequence comprises
the nucleotide sequence as shown in Fig. 4a.

8. A nucleic acid molecule according to claim 1 wherein the promoter sequence is derived from mouse TR (terc) gene promoter.

5 9. A nucleic acid molecule according to claim 8 wherein the promoter sequence is derived from the nucleotide sequence as shown in Fig. 4b.

10 10. A nucleic acid molecule according to claim 8 or claim 9 wherein the promoter sequence is at least 73bp in length starting at -22bp as shown in Fig. 4b and Fig. 5a upstream of the transcription start site.

15 11. A nucleic acid molecule according to any one of claims 8 to 10 wherein the promoter sequence comprises the construct mProm208 as shown in Fig. 4b and Fig. 5b.

20 12. A nucleic acid molecule according to any one of claims 8 to 11 wherein the promoter sequence comprises the construct mProm628 as shown in Fig. 4b and Fig. 5b.

25 13. A nucleic acid molecule according to any one of claims 8 to 12 wherein the promoter sequence comprises a nucleotide sequence as shown in Fig. 4b.

14. A nucleic acid molecule having promoter activity and being capable of hybridising under stringent conditions to the complementary sequence of a nucleic acid molecule according to any one of the preceding claims.

30 15. A nucleic acid construct comprising a TR promoter

region or a fragment, mutant, allele derivative or variant thereof able to promote transcription, operably linked to a heterologous gene.

5 16. A nucleic acid construct according to claim 15 wherein the heterologous gene encodes a cytotoxin.

10 17. A vector comprising a nucleic acid molecule according to any one of claims 1 to 14 or a nucleic acid construct according to claim 15 or claim 16.

15 18. A host cell comprising a nucleic acid molecule according to any one of claims 1 to 14 or a vector according to claim 17.

19. A host cell comprising a nucleic acid construct according to claim 15 or claim 16.

20 20. A method comprising culturing a host cell according to claim 19 under conditions for transcription of said heterologous sequence from the promoter.

25 21. A method according to claim 20 wherein the heterologous sequence is a coding sequence and the host cell is cultured under conditions for expression of the encoded peptide or polypeptide product.

30 22. A method according to claim 20 or claim 21 comprising detection of transcription of the heterologous sequence or the encoded product.

23. A method of screening for ability of a substance to modulate activity of a TR promoter, the method comprising contacting an expression system containing a nucleic acid construct according to claim 15 with a test or candidate substance and determining transcription of the heterologous sequence or expression of the encoded peptide or polypeptide product.

24. A method according to claim 23 wherein the expression system comprises a host cell containing said nucleic acid construct.

25. A method which comprises, following identification of a substance having the ability to modulate activity of a TR promoter in accordance with a method according to claim 23 or claim 24, manufacture of the substance and/or use of the substance in manufacture or formulation of a composition.

26. A substance having the ability to modulate activity of a TR promoter as determined by telomerase RNA gene expression.

27. A substance according to claim 26 which specifically blocks transcriptional activation of the TR gene promoter through interaction of the 5' regulatory sequences.

28. A substance according to claim 26 or claim 27 being selected from the group consisting of antisense oligonucleotides, transcription factors, peptide nucleic acids, and factors that disrupt signal transduction

pathways.

29. A substance according to any one of claims 26 to 28
which is Sp3 transcription factor or the CCAAT protein
complex.

30. A substance according to any one of claims 26 to 29
for use in medical treatment.

31. Use of a substance according to any one of claims 26
to 29 in the preparation of a medicament for the
treatment of cancer.

32. A substance according to claim 26 which specifically
activates the TR gene promoter through interaction with
the 5' regulatory sequences.

33. A substance according to claim 32 which is Sp1
transcription factor or pRb transcription factor.

34. Use of a substance according to claims 32 or 33 for
the preparation of a medicament for the treatment of
cancer.

35. Use of a substance according to any one of claims 26
to 29 in the preparation of a medicament for repressing
the TR gene promoter in cells.

36. Use of a substance according to claims 32 or 33 for
the preparation of a medicament for activating the TR
gene promoter in cells.

37. A vector according to claim 17 for use in a method of gene therapy.

38. Use of a vector according to claim 17 in the preparation of a medicament for the treatment of cancer.

39. A system for use in the control of neoplasia in a human or animal subject comprising a vector or other delivery system capable of selectively infecting tumour cells in said subject, said vector carrying a DNA or RNA sequence encoding an enzyme operably linked to a nucleic acid molecule according to any one of claims 1 to 14, in association with a prodrug capable of being converted to an active compound by action of said enzyme.

40. A system according to claim 39 wherein the vector is the gene therapy vector pGT62-codAupp.

41. A system according to claim 39 or 40 wherein the enzyme is viral thymidine kinase.

42. A system according to claim 39 or 41 wherein the prodrug is ganciclovir.

43. Use of a system according to any one of claims 39 to 42 in the preparation of a medicament for the treatment of neoplasia in a human or animal subject.

44. A method of treating neoplasia in a human or animal subject requiring such treatment comprising administering to the subject an effective amount of a prodrug and a

modified virus capable of selectively infecting tumour cells in said subject, said virus carrying a DNA or RNA sequence encoding an enzyme capable of converting said produg to an active compound, wherein said DNA or RNA sequence is operably linked to a nucleic acid molecule according to any one of claim 1 to 14.

45. A method according to claim 44 wherein the enzyme is viral thymidine kinase and the prodrug is ganciclovir.



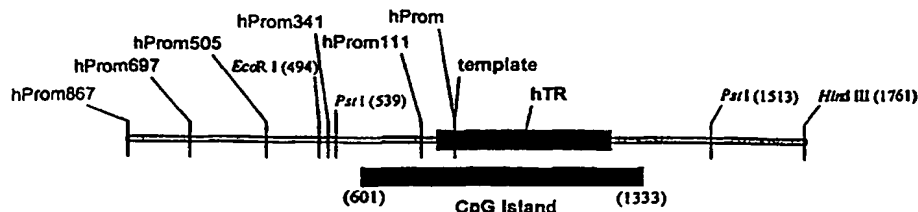
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/11, 9/12, 15/85, C12Q 1/68		A2	(11) International Publication Number: WO 99/38964
			(43) International Publication Date: 5 August 1999 (05.08.99)
(21) International Application Number: PCT/GB99/00308 (22) International Filing Date: 29 January 1999 (29.01.99) (30) Priority Data: 9801902.9 29 January 1998 (29.01.98) GB (71) Applicant (for all designated States except US): CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED [GB/GB]; Cambridge House, 6-10 Cambridge Terrace, Regent's Park, London NW1 4JL (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): KEITH, William, Nicol [GB/GB]; CRC Dept. of Medical Oncology, University of Glasgow, CRC Beatson Laboratories, Garscube Estate, Switchback Road, Glasgow G61 1BD (GB). (74) Agents: CRIPPS, Joanna, E. et al.; Mewburn Ellis, York House, 23 Kingsway, London WC2B 6HP (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.	

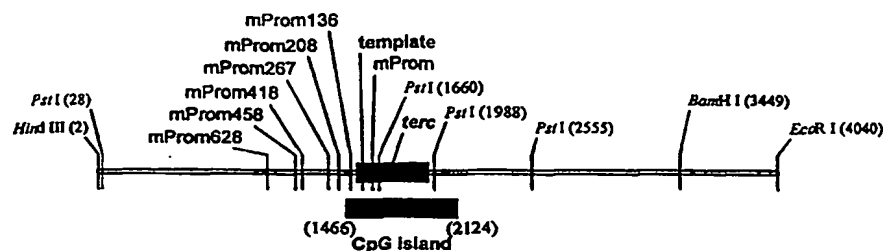
(54) Title: PROMOTER REGIONS OF THE MOUSE AND HUMAN TELOMERASE RNA COMPONENT GENES

(57) Abstract

The present invention relates to the identification of the genomic promoter region of the human and mouse telomerase RNA gene. Telomerase activity is necessary for the unrestricted proliferative capacity of many human cancers. It is proposed that mutation or dysregulation of the telomerase repression pathway may cause reactivation or upregulation of telomerase expression in cancer. The invention provides details of elements important for the regulation of telomerase RNA genes, including the Sp family of transcription factors. There is further provided methods for screening for elements having the ability for suppressing telomerase RNA gene promoter activity and use of such elements in the treatment of cancers. In addition, evidence is also provided for the development of new transcription based therapies for cancer and for genetic approaches to targeting therapeutic genes to cancer cells. Namely, (1) transcriptional repression and the disruption of signal transduction pathways regulating telomerase activation. (2) Tumour specific gene expression for genetic therapy via telomerase RNA gene promoters.



A



B

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

1/29

1 agctactcag gaggctgaga cacgagaatc gcttgaaccc gggaggcaga ggttgacgtg
 61 agccgagatc acgccactag actccatcca gcttggcga aagagcaaga ctccgtctca
 121 aaaaaaaaaa tcgttacaat ttatggtgga ttactccctt tttttacct catcaagaca
 181 cagcactact ttaaaagcaa gtcaatgatt gaaacgcctt tctttcctaa taaaagggag
 241 attcagtcct taagattaat aatgtagtag ttacacttga ttaaagccat cctctgctca
 301 aggagaagct ggagaaggca ttctaaggaa aaaggggcag ggttggaact cggacgcac
 361 cactagacc gagacaagat tctgctgtag tcaagtgtgc ctgggaatct attttcaca
 421 agttctccaa aaaatgtgat gatcaaaact aggaattagt gttctgtgtc ttaggcctca
 481 aaatcttct gtgaattcca tttttaaggt agtcgaggtg aaccgcgtct ggtctgcaga
 541 gtagaagaaa aaggccctct gatacctcaa gtagtttca cctttaaaga aggtcggaag
 601 taaagacgca aagcctttcc cggacgtgcg gaagggaac gtccttctc atggccgga
 661 atggaacttt aatttccgt tcccccaac cagccgcgc gtagagatga ctctcacgag
 721 agccgcgaga gtcagcttgg ccaatccgtg cggtcggcg ggtcgcctt tataagccga
 781 ctgcgccggc agcgcaccgg gttgcggagg gtgggcctgg gagggtggt ggcattttt
 841 tgtctaacc taactgagaa ggcgtaggc cccgtgctt tgcctccgc gcgctgttt
 901 tctcgtgac tttagcggg cggaaaagcc tcggcctgcc gcttccacc gttcattcta
 961 gagcaaaaa aaaatgtcag ctgctggccc gttcgccct ccggtggacc tgcggcgggt
 1021 cgcctgccc gccccgaac cccgcctgga ggcccggtc ggcccggggc ttctccggag
 1081 gcactactg ccaccgcga gagttggctc tgtcagcgc aggaacggag cgagtcctcg
 1141 cgaggttcag gcctttcagg cgcaggaag aggaacggag ggtctctcg gggcgaggg
 1201 gattccctga gctgtggac gtgcaccag gactcggct acacatgcag ttcgcttcc
 1261 tgttggtgg gggaacgcc atcgtgcga tccgtcacc ctgcgggca gtgggggctt
 1321 gtgaacccc aaacctgact gactgggcca gtgtgctga aattggcagg agacgtgaag
 1381 gcacctccaa agtcggccaa aatgaatgg cagtgcgcg ggttgcctg gagccgttcc
 1441 tgcgtgggtt ctccgtctt cgcctttttg ttgccttta tgggtgtatt acaacttagt
 1501 tctgctctg cagattttgt tgaggttttt gcttctcca aggtagatct cgaccagtcc
 1561 cctcaacggg gtgtgggaga acagtcat ttttttga gatcattaa catttaatga
 1621 atatttaatt agaagatcta aatgaacatt gaaaattgt ttcctttaat ggtcatcggt
 1681 ttatgccaga ggttagaagt tctttttttg aaaaattaga ccttggcgat gaccttgagc
 1741 agtaggatat aacccccaca agctt

Fig. 1

2/29

```
1 aagcttggac ttgacaaaga aactgcagat catctggacc ccccccccc cccatttagg
61 ttttaacaatg taccagctat ctgacttaag caaactgtgt tcctcataga taaggcggga
121 ctgctcatgg tcattgtgaa gttcagttgg gataaacaata ttttaagggtg cataacaaaa
181 aacacaaaat gttggtgttt gtttaaaaaa aactaaagaa tttctggagg caggcagtta
241 cagaaaacat gctgatattc tgagttgcct gctagttggt gccattccac cagagtgaac
301 acatctctgt tgaccctgat tttctgtagg tctgtctgtg tgtctgtcct ttctccagca
361 agggctgacc ctaatcgggg tcccaggacc caagccttga gaaaggcagt agtatgtcat
421 ctagttgaaa tgacacattc tctacagtgt ccaaatagaca tctttgtgct agacagaaca
481 ttttattgga tggactatgg ctgaccactt ggcttggggg gggggggaag gggccgcca
541 gggcgggggt ccctcatttg cttgttatta acacttgctt gttgttttac ttgttagtag
601 gaatctgctc taccacgtgg gttctacatg gttccacagg ggtcacctgg tccgtttttg
661 ttttctggga cagttttcac aaatgttgct tagactccac gttggctttg aagcctacag
721 ctatgagcct ctgtgccagt ttatgcagta gtatctctcg ggttgctcct caccgttagt
781 agtggtgctc ttagaaggca ccgtgatttt ttgctttcca tctctttccc ctgccatgcc
841 ttctgtggtt ctctgccagg caccaaactg ttcagaaact ctccagcccc gtagagaacg
901 gtagggggaa agaactgacg tgtggaaggg atgggcaggg agaagaggca ccgaactcgg
961 tcttaacaaa aaaaaaaaaa aaaaggagca ttagaaaaaa aaacaaattt gtgacctga
1021 actacagacc tcctgcctca gcctcctaca agctgggatt ataggctcgg gtcagctacc
1081 cttgaaatct ttttctttct ggaactcagt acctgggtgg ccatgcactc acaagagatc
1141 cgctgcctt ctgtctctca aattctggaa ttaaagattt gcgccattt tccccattc
1201 cccccggc tgtgggagtg gactgggttg aagtggaat ttttttttt ttttttttt
1261 tttagtga aaagggggga ttggaaatat cctactttc aactctagta ttttcagaa
1321 accaagcctc agagatgtgc gtgcgtgcgt gtgtgtgtgt gtatgtgtgt gtgtctcaca
1381 gcaagaaaca gattttatta tttatttttt atttatttat tttttgcaag tgactggcta
1441 ggaagagtgg ggaagcggga ggacaaatgg ggaagaggga gcatttccgc aagtgtggtg
1501 ctcgaccaat cagcgcgcgc catggggtat ttaaggtcga gggcggctag gcctcggcac
1561 ctaaccctga ttttcattag ctgtgggttc tggctttttg ttctccgccc gctgtttttc
1621 tcgctgactt ccagcgggcc aggaaagtcc agacctgcag cgggccaccg cgcgttcccg
1681 agcctcaaaa acaaacgtca gcgcaggagc tccaggttcg ccgggagctc cgcggcgccg
1741 ggccgcccag tcccgtacct gcctacaggc cgcggccggc ctgggggtctt aggactccgc
1801 tgccgcccgc aagagctcgc ctctgtcagc cgcggggcgc cgggggtctg ggccaggccg
1861 ggcgagcgcc gcgaaggaca ggaatggaac tgggtccccgt gttcgggtgtc ttacctgagc
1921 tgtgggaagt gcacccggaa ctcggttctc acaaccccca tccccgttg ggaaatgcc
1981 cgctgcaggg cgggcccgtc gaacctgcga cttctgggga aaggggttc ggtgtgagac
2041 ggtagccagc caaagggtat atatcgccct cagccccgt cccctccac tttgtctaa
2101 tactcctgtt tctgttgtgc agattttgca ggcgtttcgc tggctctgcc tgaacgagct
2161 atgcagccat gtggtccttg ggggtggggg tggggatggg aggactacag gcgtagatct
2221 tcatactggg tttgtgtagt gctgggaatt gaacctagtt tctaagttc tctatcaact
```

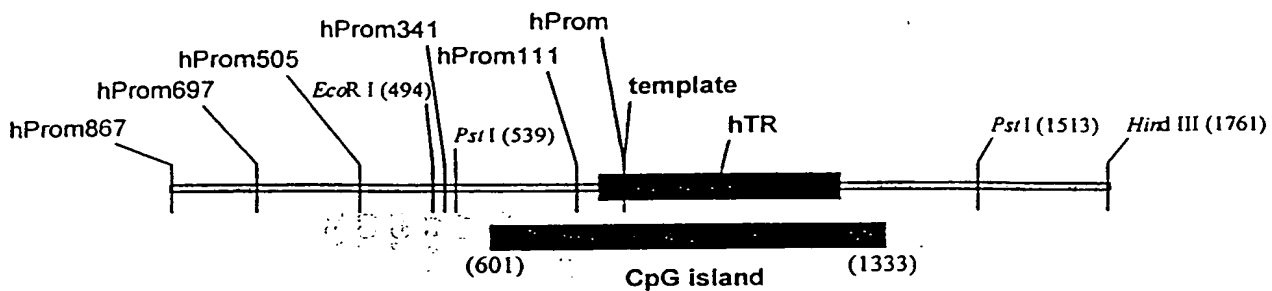
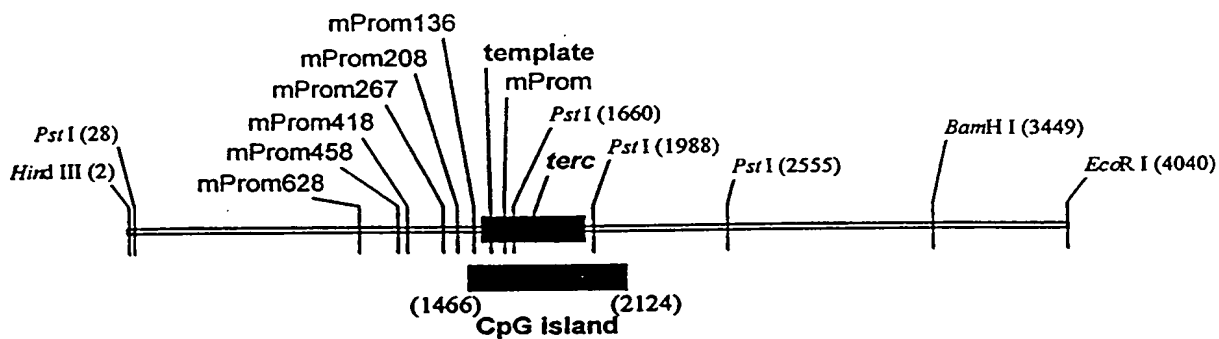
Fig. 2

3/29

```
2281 ggtattccca ttgtatggga gatttttttt ttcttttgta tatgggggcg ttgaacattt
2341 tgtaaacaat tagaaaatct agtagttttt taatgaaaat gttcactttt ctttgtcttt
2401 gggatgcaaa acattacatt gaagctgaga agtttaaaga tgcgtgtctt cccctgccta
2461 ccttcgcgtt cacacagaac ctgttatctt ttcagaaaag aaaatgagat aggcagggtg
2521 gatctggagt ttcaaggccc ttgcctggtc tgcagagtga gttaggccac accagaaaag
2581 tatgtgtcaa aaacaaagaa gaaaggcttt gtggggggtg gggtagcaaa cgatcttaat
2641 cccctgtgct tgggaggccc gcaaggggga tatctgtgaa ggagacaaac aaagctacac
2701 tgtgtggtaa acaaaaaacg aggaggagga gcaagaagaa tatgagagcc cacggaagga
2761 agagtatcag tccccaggcc accagttcct caggggtaac tatgtttgtg agtgtctcgg
2821 tgccttgact tcctcagtac ttttctgggt tttagtcata aaaaacattg aagagatgaa
2881 gaagtgtatg tttagtaagt acataccaaa agtttgtgag ctatatgcat atagcaactc
2941 agtcacctga aacaggcccc ttgcagctaa catatttctt agtattacta ttataaagac
3001 taggggagtt tctaagccgg cactccttac aagggacgaa gccatgttca gctccagctt
3061 gccaaagattc tgaaacccaa cgtcaagcct gacgagttcg agcctggcat ctctcagccg
3121 ctgctcgagc tggagatgac cacggatctc aaggcacagc tgtgggaact caacatcacc
3181 gaagccaagg aaaattgaag ttggtggtgg tcagaaggct gttataattt ttgtaccagt
3241 tcctcagctt aaatctttcc agaaaatcca agtctggcta gtttgtgaat tggagaaaaa
3301 gttcagcgga aagcacgtgt cttcattgct cagaagagga tctgtccaag ccaaccagga
3361 aaagctgtac gaaaaataag ccaaagcacc ctagaagctg caccctgaca gcagtgcattg
3421 tcttctcaag tgaaattgtg ggaaagagga tccatcctg tgaactgga tggcaatctg
3481 gagcaggttc atcttcctct ctggtacatc ccatgtctcc tcatctccat cctcccctct
3541 gcctctgtgt ctcatctcta aaactctcag cccatcttcc tttaccactg cccaatcaca
3601 ggctctagcc ttacctttca cctgccctca cctgcttata gacagcaatc tacatttctc
3661 cctttttgtc caattaaaag actcttttct ctcgatata aaatgagcac aactattatt
3721 accattctgt aatttataaa gtatagatag acctaacacc cagtctatca ttttgacagt
3781 taaataaagc attctgcaat cctatcctaa ctttaaaagg cttataattc tacacttggt
3841 atgtcctggt tcagcttgta tattagaaaa ccatctcaaa ttatatatat atatatatta
3901 cacacacaca tatgtatata tacatatata tgtatacaca cacacacata tatatatgta
3961 tatgtatgta tgtatgtata tatatatact tttaatgcta aatagcctgg gttggctaag
4021 actacttcaa tcctgccaga attc
```

Fig. 2 (cont)

4/29

*Fig. 3A**Fig. 3B*

5/29

taactgagaagggcgtat^{hProm}

Fig. 4A

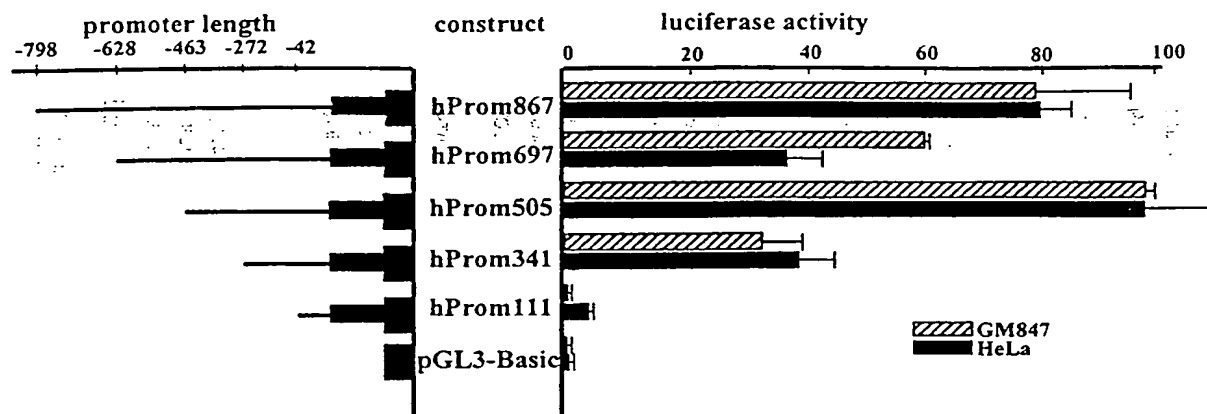
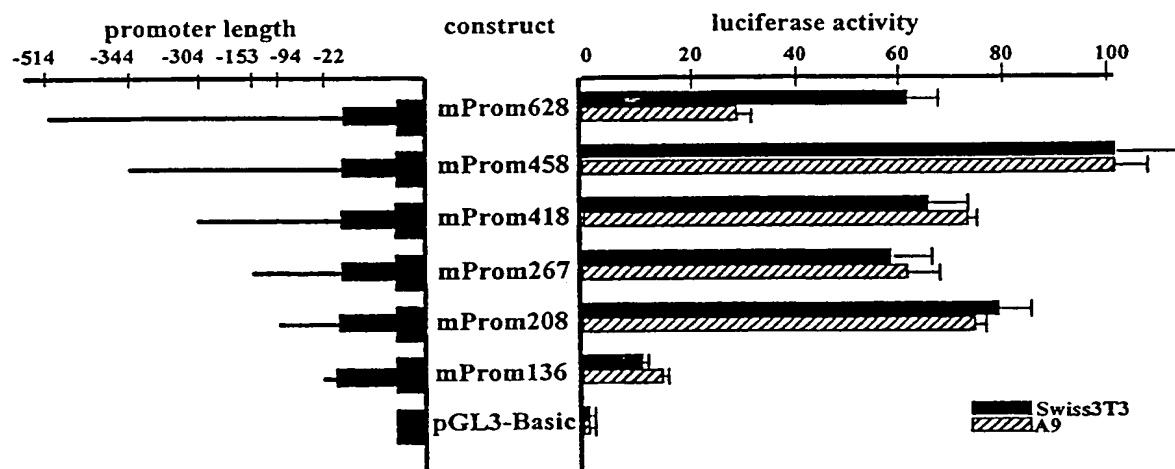
6/29

-531 ^{mProm628} tgtgaccttgaactacagacctcctgcctcagcctcctacaagctgggat
 PPAR/ELP GR
 -481 tataggctcgggtcagctacccttgaaatcttttctttctggaactcag
 H4TF-1
 -431 tacctggttgccatgcactcacaagagatccgcccgccttctgtctctc
 API/GCN4/Zeste SP-1
 -381 aaattctggaattaaagattgcccacttttccccacttccacccccgg
 ^{mProm458}
 C/EBPalpha, beta AP-2
 -331 ctgtgggagtggaactgggttgaaagtgaatttttttttttttttttt
 ^{mProm418}
 p300
 -281 ttttagtgaaaaaaggggggattggaaatatccctactttcaactctagt
 CPI
 -231 atatttcagaaaccaagcctcagagatgtgcgtgcgtgcgtgtgtgtgtg
 -181 ^{mProm267} gttatgtgtgtgtgtctcacagcaagaaacagattttattatttttt
 GR F2F/Pit-1a
 -131 tattttatttttttttgcagtgtgactgggtaggaagagtggggaagcggg
 ^{mProm208}
 IRF-1,2 GCN4/AP1 AP-2 c-ETS-2
 -81 aggacaaatggggaagaggagcatttccgcaagtgtgtgggtcgaccaa
 GR AP-2 c-ETS-2 ^{mProm136} CCAAT Box/AP-1
 -31 tcagcgcgcgccatgggggtatttaaggtcgagggcggtaggcctcgga

cctaaccctgattttcattagctgtgggttctggtcttttgttctccgcc
 template
 cgctgtttttctcgtgacttccagcgg ^{mProm}

Fig. 4B

7/29

*Fig. 5A**Fig. 5B*

8/29

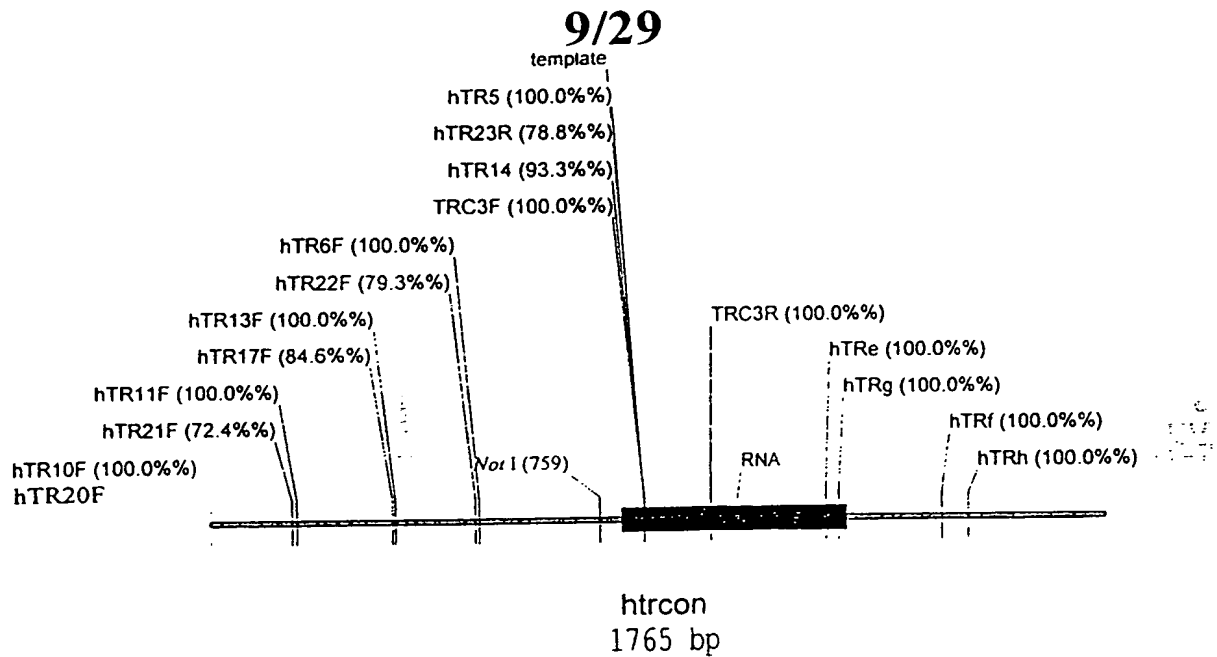
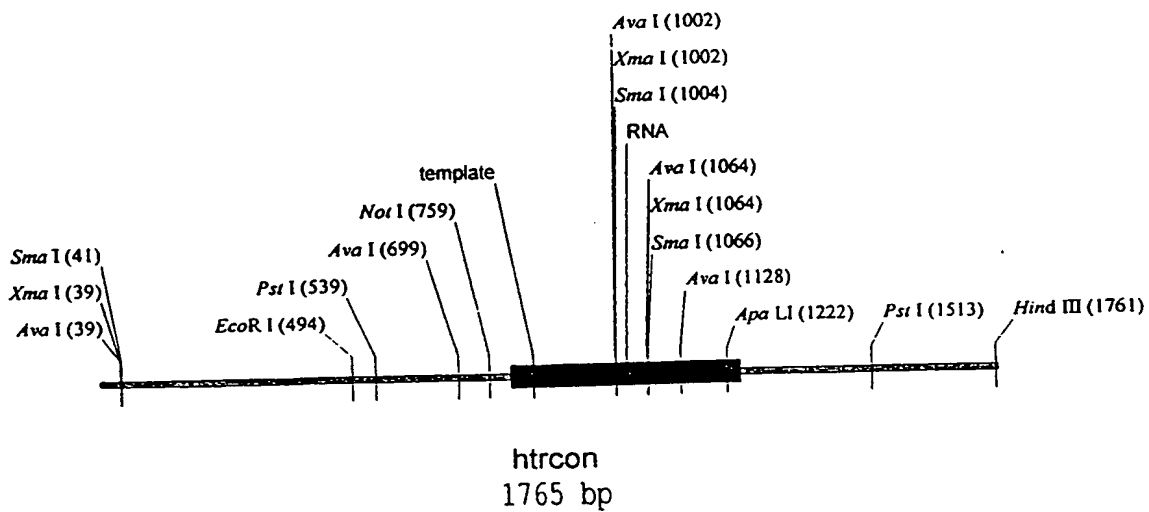
Oligo's Used: human

Name	Sequence	Comments
hTR5	TACGCCCTTCTCAGTTAGGGTTAG	
hTR14	GGATCCTACGCCCTTCTCAGTTAGGGTTAG	hTR5 with BamHI site
hTR13F	ACTGAGCCGAGACAAGATTC	
hTR17F	GGATCCACTGAGCCGAGACAAGATTC	hTR13F with BamHI site
hTR10F	AGCTACTCAGGAGGCTGAGA	
hTR20F	GCGCTCGAGAGCTACTCAGGAGGCTGAGA	hTR10F with XhoI site plus gcg clamp
hTR11F	CATCAAGACACAGCACTACT	
hTR21F	GCGCTCGAGCATCAAGACACAGCACTACT	hTR11F with XhoI site plus gcg clamp
hTR6F	GTCTGGTCTGCAGAGGATAG	
hTR22F	GCGCTCGAGGTCTGGTCTGCAGAGGATAG	hTR6F with Xho site plus gcg clamp
hTR5	TACGCCCTTCTCAGTTAGGGTTAG	
hTR23R	CGCAAGCTTTACGCCCTTCTCAGTTAGGGTTAG	hTR5 with HindIII site plus cgc clamp
hTRe	CTGAGCTGTGGGACGTGCAC	
hTRf	AGACGGGAGAACCCACGCAG	
hTRg	CTCGGCTCACACATGCAGTT	
hTRh	TCTGCAGAGCAGGAAGTAAGT	
TRC3F	CTAACCCTAACTGAGAAGGGCGTA	
TRC3R	GGCGAACGGGCCAGCAGCTGACATT	

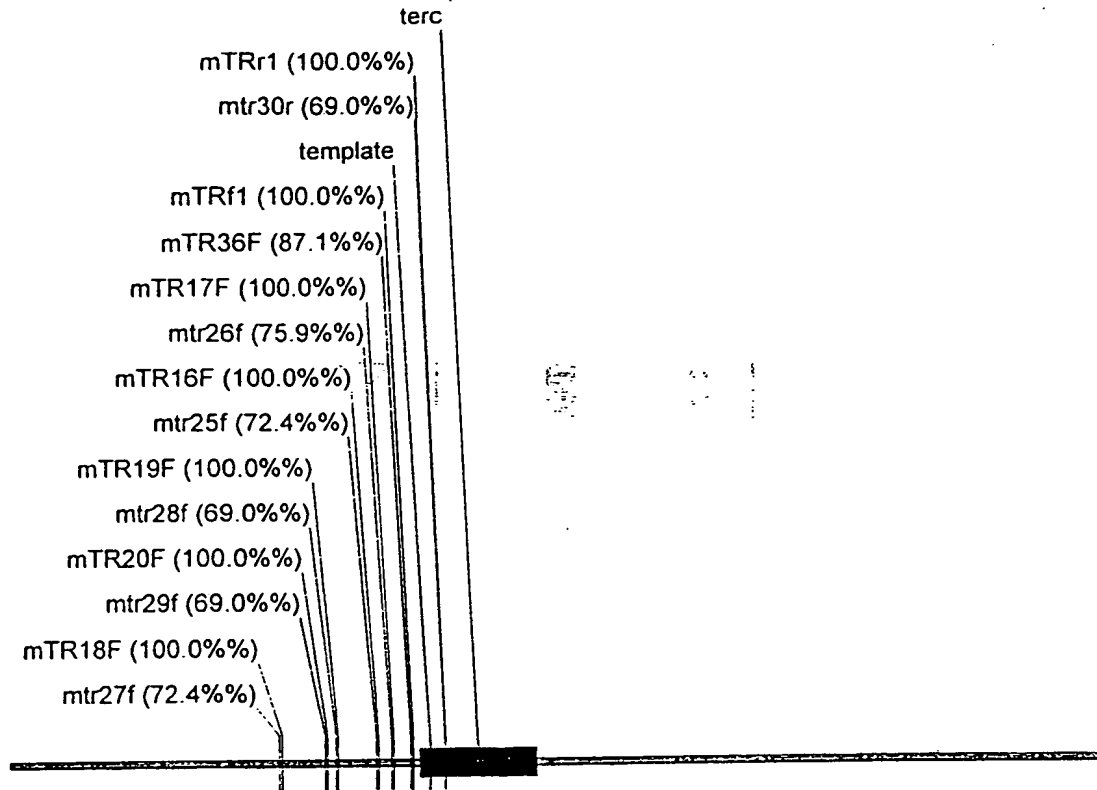
Oligo's Used: Mouse

Name	Sequence	Comments
mTR16F	GTGTCTCACAGCAAGAAACA	
mtr25f	GCGCTCGAGGTGTCTCACAGCAAGAAACA	This is mtr16f with XhoI site plus gcg clamp
mTR17F	GTGACTGGCTAGGAAGAGTG	
mtr26f	GCGCTCGAGGTGACTGGCTAGGAAGAGTG	This is mtr17f with XhoI site plus gcg clamp
mTR18F	TGTGACCTTGAAGTACAGAC	
mtr27f	GCGCTCGAGTGTGACCTTGAAGTACAGAC	This is mtr18f with XhoI site plus gcg clamp
mTR19F	GGACTGGGTTGAAGGTGGAA	
mtr28f	GCGCTCGAGGGACTGGGTTGAAGGTGGAA	This is mtr19f with XhoI site plus gcg clamp
mTR20F	TGCGCCACTTTTCCCCACTT	
mtr29f	GCGCTCGAGTGCGCCACTTTTCCCCACTT	This is mtr20f with XhoI site plus gcg clamp
mTRr1	CCGCTGGAAGTCAGCGAGAA	
mtr30r	CGCAAGCTTCCGCTGGAAGTCAGCGAGAA	This is mTRr1 with HindIII site plus cgc clamp
mTR36F	GCGCTCGAGTCGACCAATCAGCGCGGCCAT	This is Xho I site PCR primer plus gcg clamp
mTRr1	CCGCTGGAAGTCAGCGAGAA	
mTRf1	TCGACCAATCAGCGCGGCCAT	

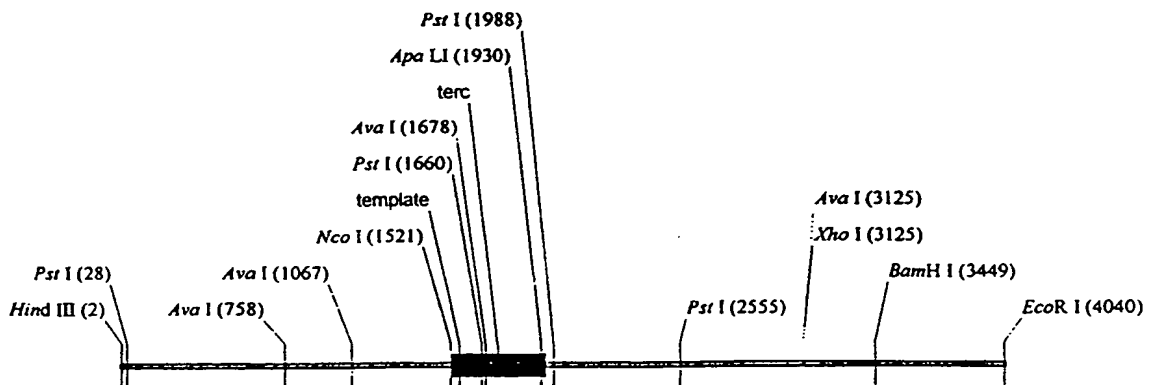
Fig. 6

**Fig. 7A****Fig. 7B**

10/29



tercCon
4044 bp

Fig. 8A

tercCon
4044 bp

Fig. 8B

12/29

<i>Human Promoter</i>
TATA
CCAAT
SP-1
API
PEA2/PEBP2
PU.1
PEA3
GATA1
C-MYB
GR/PR/AR
F2F
ZESTE

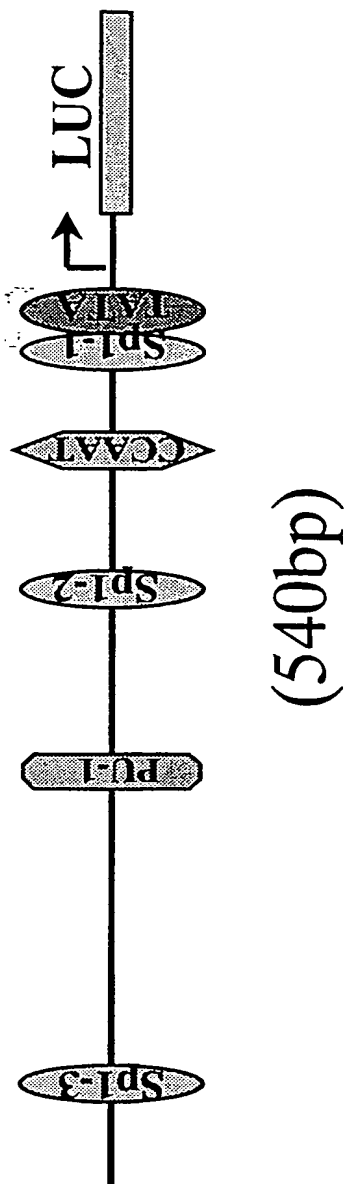


Fig. 10

[illegible]

Fig. 11

14/29

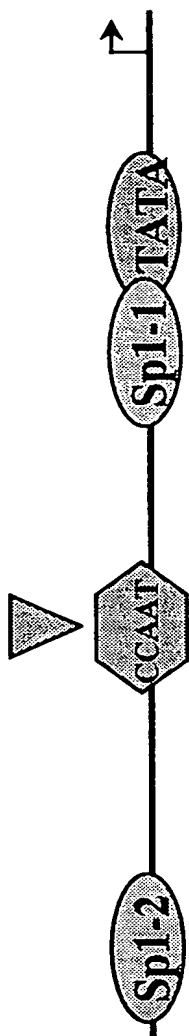
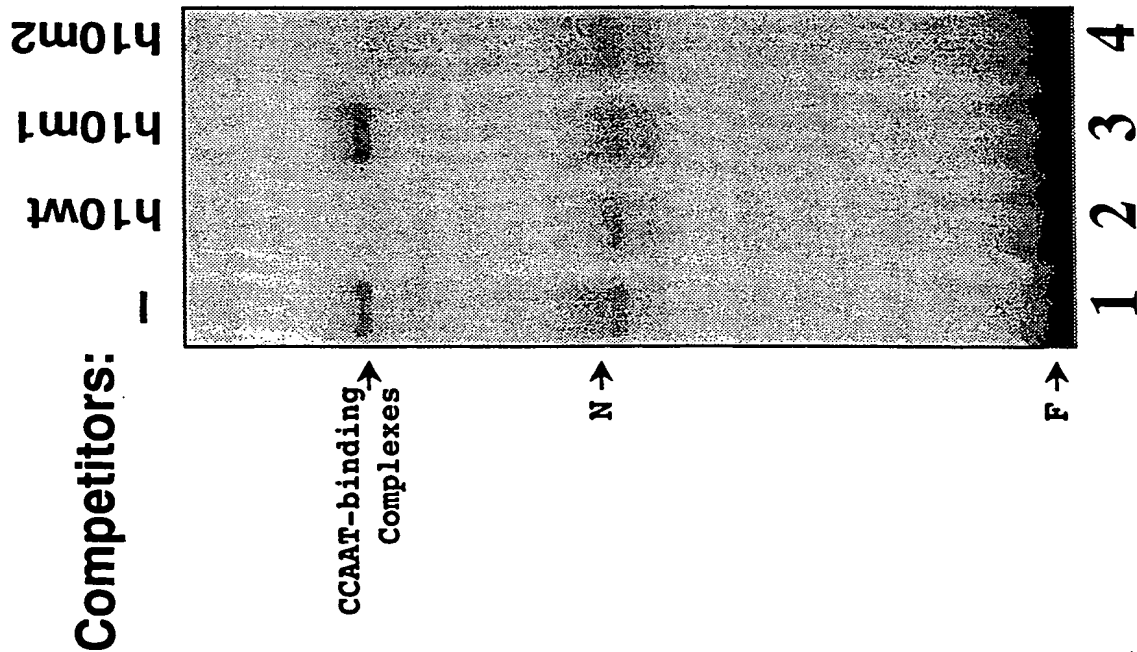
Oligonucleotide	Position	Sequence*	Purpose
h11 ^a	-2 to +36	CCGGGTTGCGGAGGCTGGGCTGGAGGGGTGGTGGCC	RCE(+12, +16 and +30, +34) and Sp1.4 binding site
h111 ^a	"	CCGGGTTGCGGAAATGGGCTGGAGGGGTGGTGGCC	RCE1 mutation from ggg to aaa (+11/+13)
h112 ^a	"	CCGGGTTGCGGAGGCTGGGCTGGGTAAGGTGGTGGCC	Sp1.4 mutation from agg to taa (+24/+26)
h113 ^a	"	CCGGGTTGCGGAAATGGGCTGGGTAAGGTGGTGGCC	Mutant of both RCE1 and Sp1.4 binding site(+11/+13, +24/+26)
h11c ^a	-2 to +23	CCGGGTTGCGGAGGCTGGGCTGGG	RCE1 binding site
H11d ^a	+14 to +36	GCCTGGAGGGGTGGTGGCC	Sp1.4 or RCE2 binding site
h111a ^{ab}	"	CCGGGTTGCGGAAATGGGCTGGG	RCE1 mutation from ggg to aaa(+11/+13)
h112b ^{ab}	+15 to +36	GGGCTGGGTAAGGTGGTGGCC	Sp1.4 mutation from agg to taa
h112c ^{ab}	"	GGGCTGGGTAAGGTAATGGCC	Sp1.4 and RCE2 mutant from aggggtgg to laagtaa(+24/+26, +30/+31)
h11e ^a	"	GGGCTGGGAGGGTAATGGCC	RCE2 mutant from gg to (+30/+31)
h10 ^a	-63 to -42	CTTGGCCAATCCGTCGGTCGG	h10 footprinting region containing CCAAT binding site
h101 ^a	-63 to -42	CTTGGAGTCTCCGTCGGTCGG	CCAAT motif mutation from ccaa to agtc, (-58/-55)
h10m1 ^b	-74 to -45	GCGAGAGTCAGCTGGAGTCTCCGTCGG	CCAAT motif mutation from ccaa to agtc, (-58/-55)
h10m2 ^{ab}	-63 to -42	CTTGGCCAATCCTGATGTCGG	h10 mutation from gtgc to tgat, (-51/-47)
h9 ^a	-44 to -17	CGCGGCGCGTCCCTTTAAGCGGACT	h9 footprinting region containing SP1.1 binding site
h91 ^a	-44 to -21	CTTAAGCGCGTCCCTTTAAGCC	h9 mutation from ggcg to ttac, (-43/-40)
h910 ^b	-53 to -29	CCGTGCGGCTTACGCGGCTCCC	h9 mutation from ggcg to ttac, (-43/-40)
h911 ^a	-44 to -21	CGCGTAACCTCCCTTTAAGCC	h9 mutation from ggcg to taaa, (-39/-36)
h92 ^a	-44 to -21	CGCGGCGCATAGCCTTTAAGCC	h9 mutation from gtc to atag, (-36/-33)
h921 ^a	-44 to -21	CGCGGCGGCTCATGCTTAAGCC	h9 mutation from cctt to atgc, (-32/-29)
h93 ^a	-44 to -21	CGCGGCGGCTCCCTTCGACAGCC	h9 mutation from tata to cgac, (-28/-25)
h930 ^b	-38 to -14	CCGCTCCCTTCGACAGCCGACTCGC	h9 mutation from tata to cgac, (-28/-25)
h4 ^a	-110 to -91	ACCAGCCGCGCGAGAGAGT	h4 footprinting region containing SP1.2 binding site
h41m ^a	-110 to -91	ACCAGCCGCGACGAGAGAGT	Sp1.2 mutation from cc to aa, (-101/-100)
h5 ^a	-471 to -452	GAAAAGGGGAGGTTGGA	SP1.3 binding site
h5m ^a	-471 to -452	GAAAAGGTTTCAGGGTTGGA	Sp1.3 mutation from gg to tt, (-463/-462)

* Nucleotides corresponding to promoter sequences are given in uppercase letters from 5' end to 3' end; specific nucleotides mentioned in Purpose column are underlined. Highlight indicate mutagenesis nucleotide.

^a Complementary lowerstrand sequence for EMSA not shown.

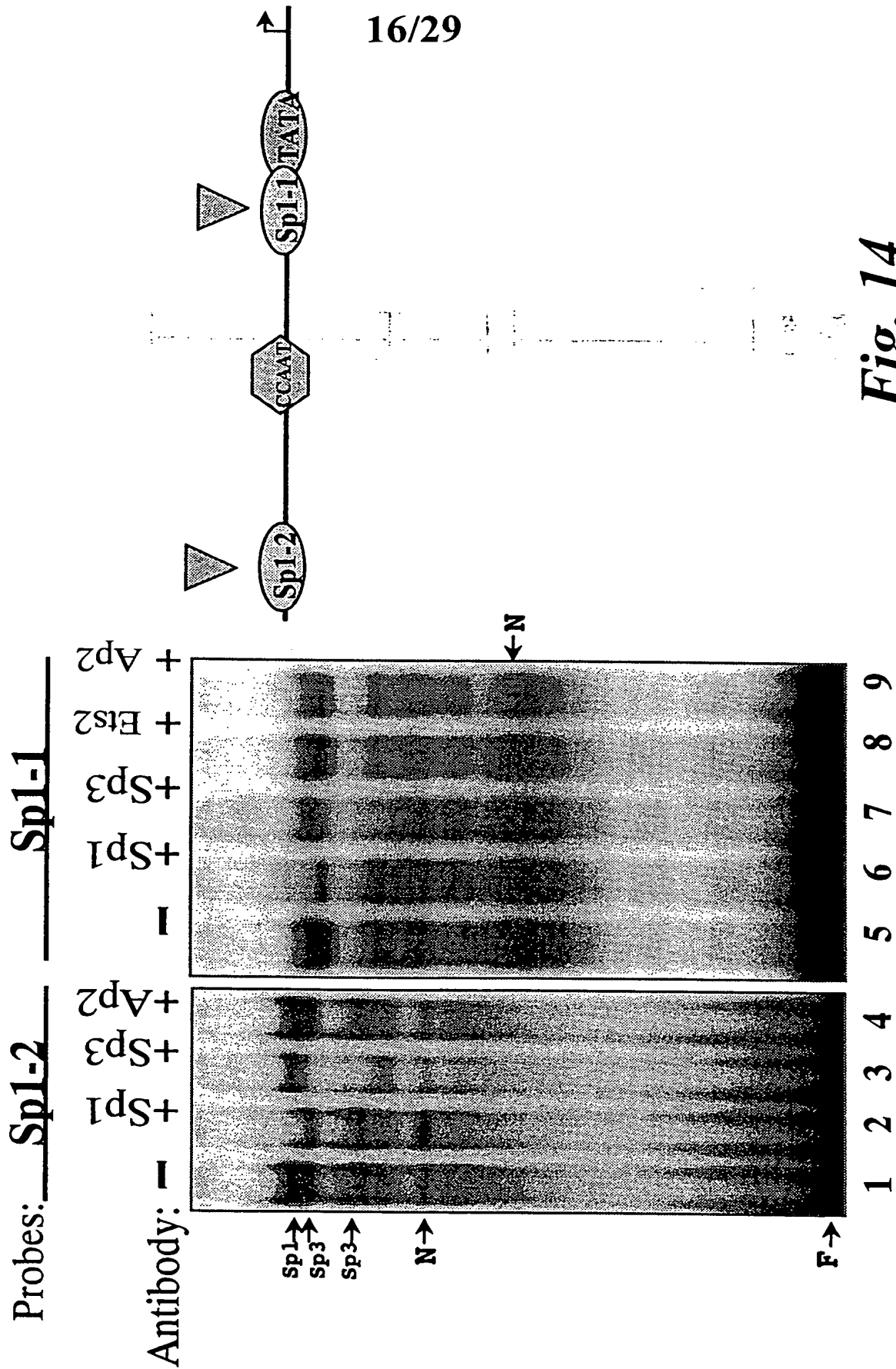
^b For PCR-directed in vitro mutagenesis, complementary lowerstrand sequence not shown.

Fig. 12



h10 (wt:-63 -42)	CTTGGCCAATCCGTGCGGTCGG
h10m1 (-58 -55)	:::AGTC:::::::::
h10m2 (-51 -47)	:::TGAT:::::::::

Fig. 13



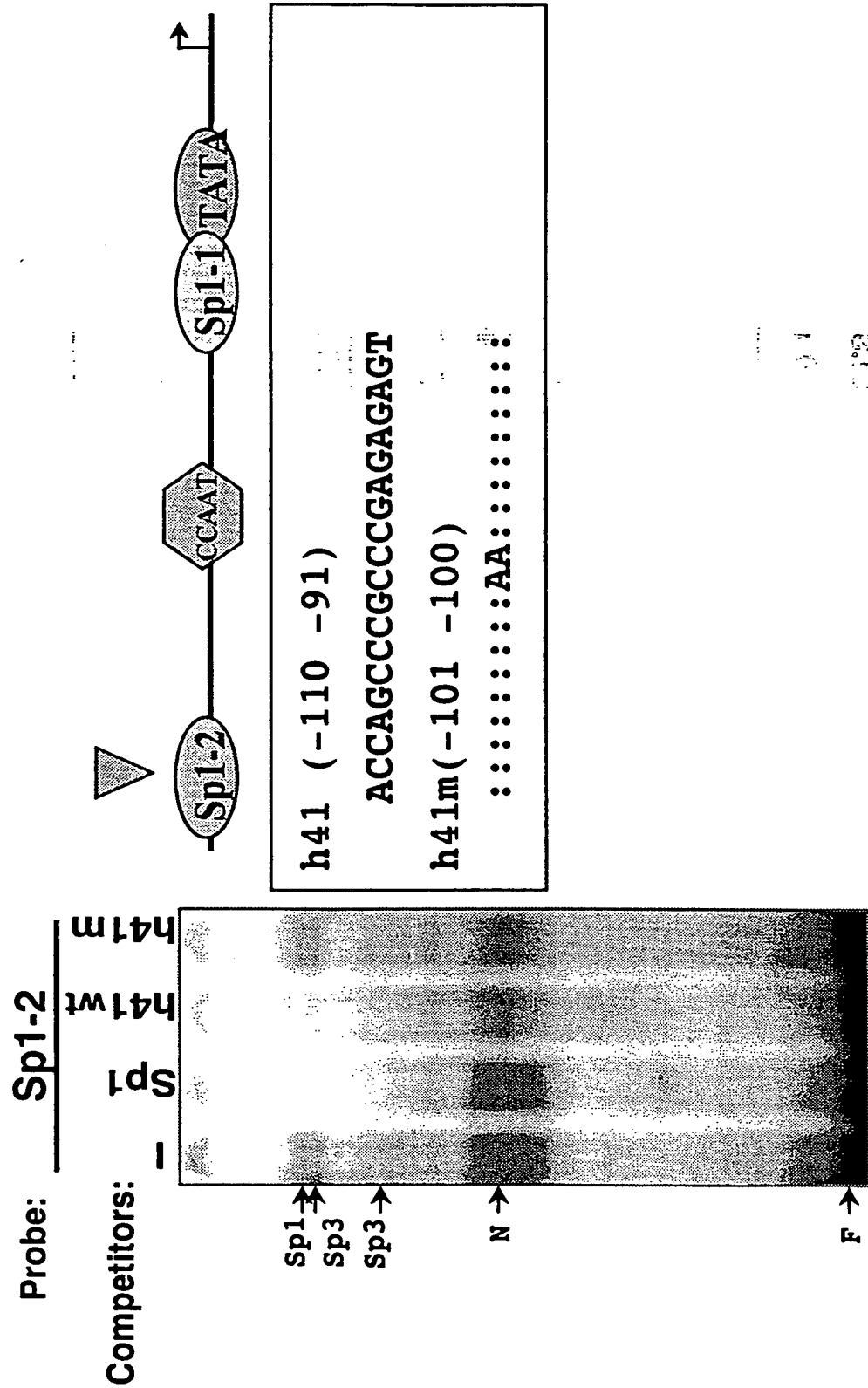


Fig. 15

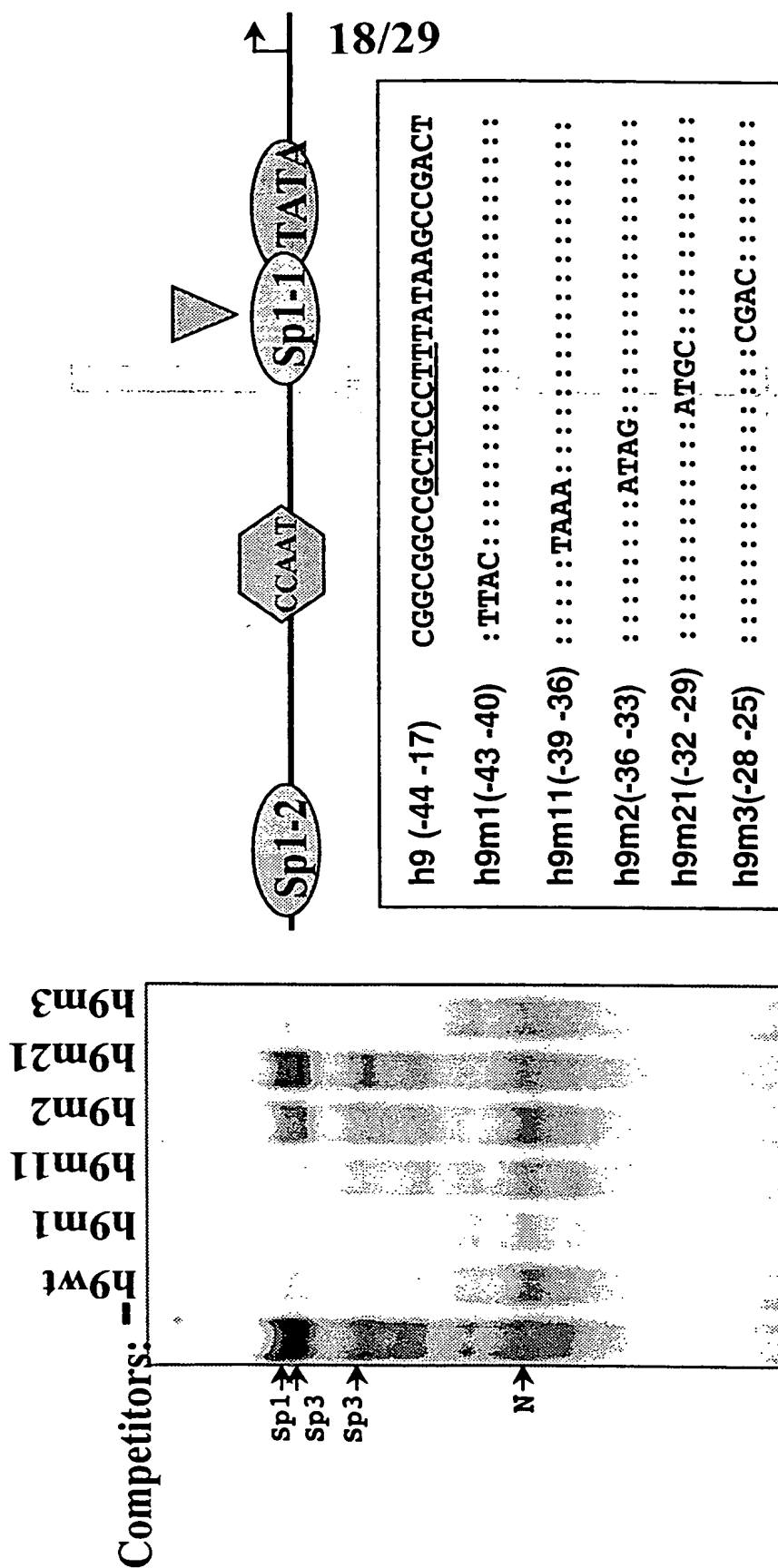
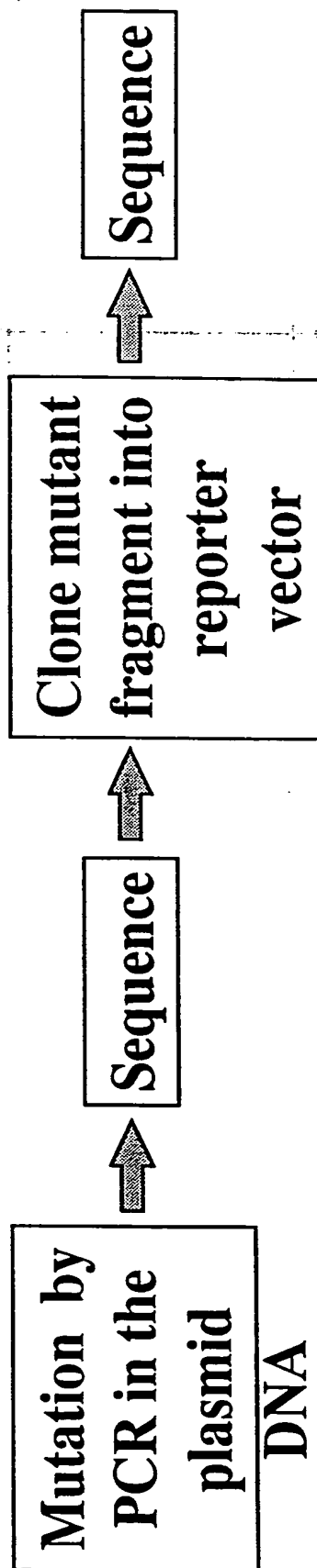


Fig. 16

19/29



- Gel shift assays identify DNA/protein binding activity
- Do mutation of these binding sites influence the promoter activity?

*Fig. 17*

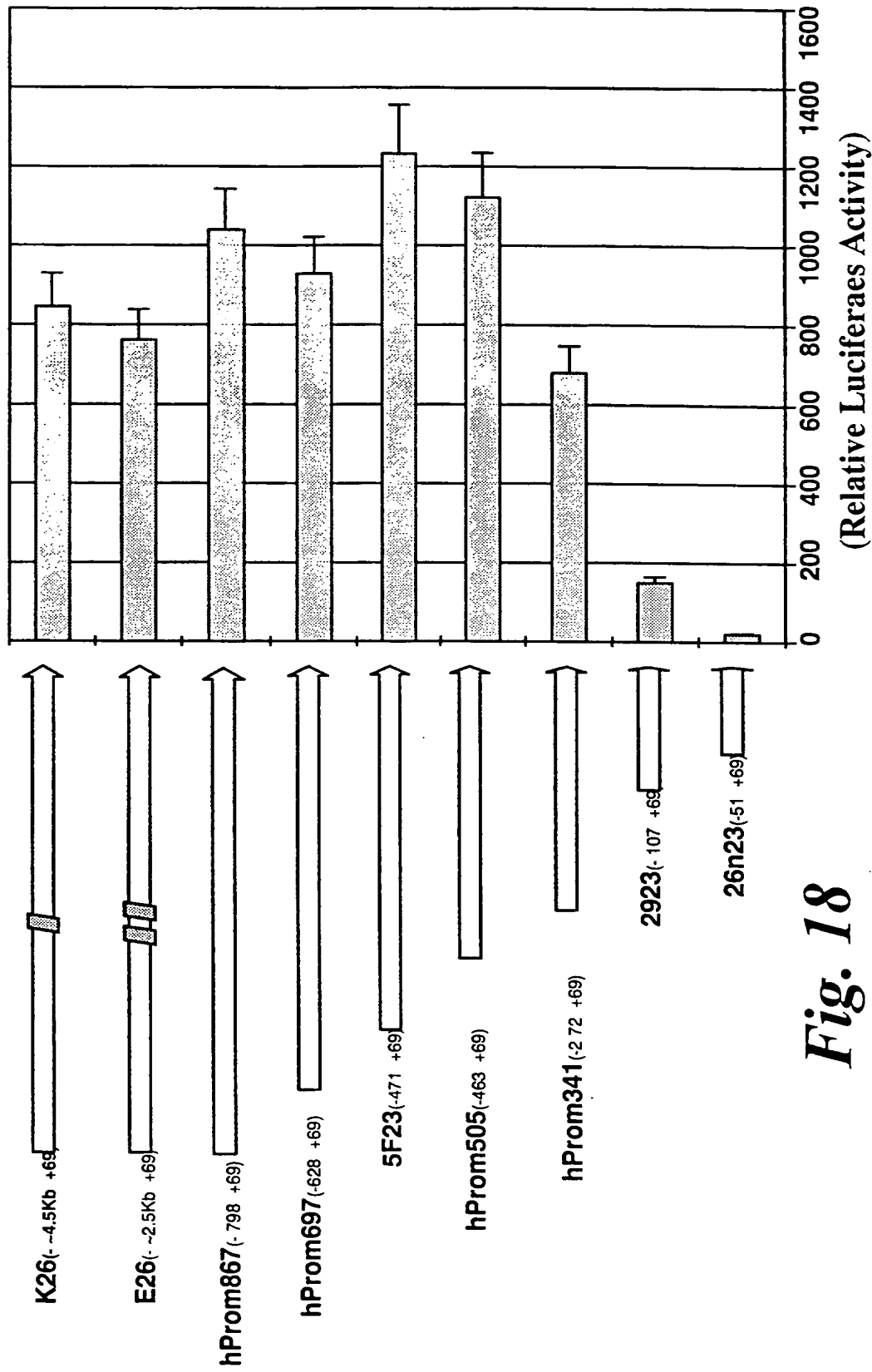


Fig. 18

21/29

G E N E S E Q U E N C E

```

-107                                     -55
2923(-107 +69)  AGCCCGCCCCGAGAGAGTGACTCTCACGAGAGCCGCGAGAGTCAGCTTGGCCAA
29m23(mSp1.2)   -----AA-----
1011                                     -----AGTC
29m292(mSp1-1,2) -----AA-----
29m921(mSp1-1,2) -----AA-----

-54                                     -1
2923(-107 +69)  TCCGTGCGGTCGGCGGCCGCTCCCTTTATAAGCCGACTCGCCCGGCAGCGCACC
102             ---TGAT-----
910             -----TTAC-----
911             -----TAAA-----
92(mSp1.1)      -----ATAG-----
29m292(mSp1-1,2) -----ATAG-----
921(mSp1.1)     -----ATGC-----
29m921(mSp1-1,2) -----ATGC-----
930(mTATA)      -----CGAC-----
26n23(-51 +69)  -----

+1                                     +53
26n23(-51 +69)  GGGTTGCGGAGGGTGGGCCTGGGAGGGGTGGTGGCCATTTTTTGTCTAACC
29111(mRCE)     -----AAA-----
29112(mSp1.4)   -----TAA-----
111(Sp1.4)*     --//--//--AAA-----
112(RCE)*       --//--//--TAA-----
113(mSp1+mRCE)* --//--//--AAA-----TAA-----
115*            --//--//--TAA--AA-----
114*            --//--//--AAA-----TAA--AA-----

+54                                     +69
CTAACTGAGAAGGGCGTA

```

* Double mutagenesis by using pLh29m292 as template.

Fig. 19

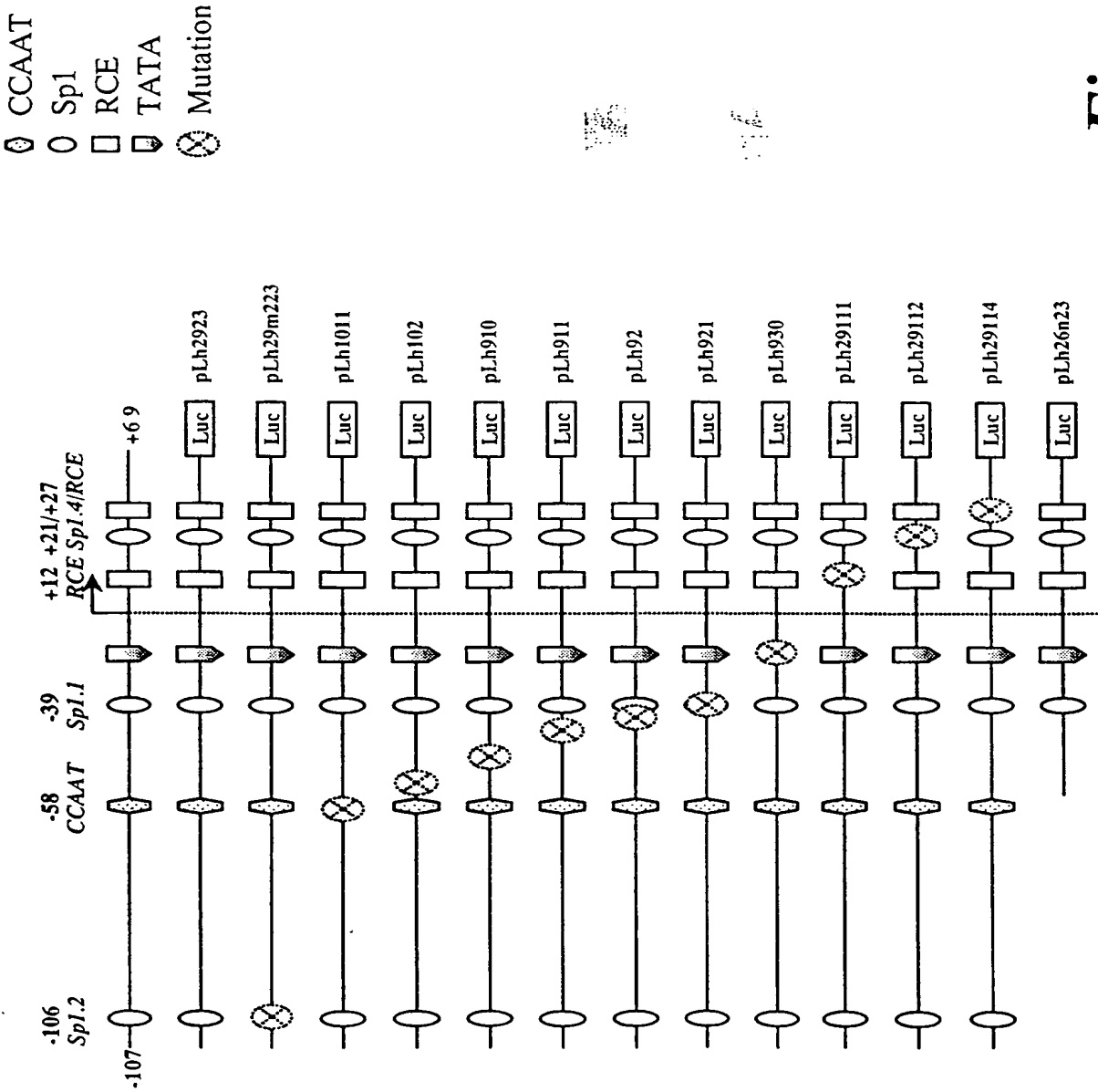


Fig. 20

23/29

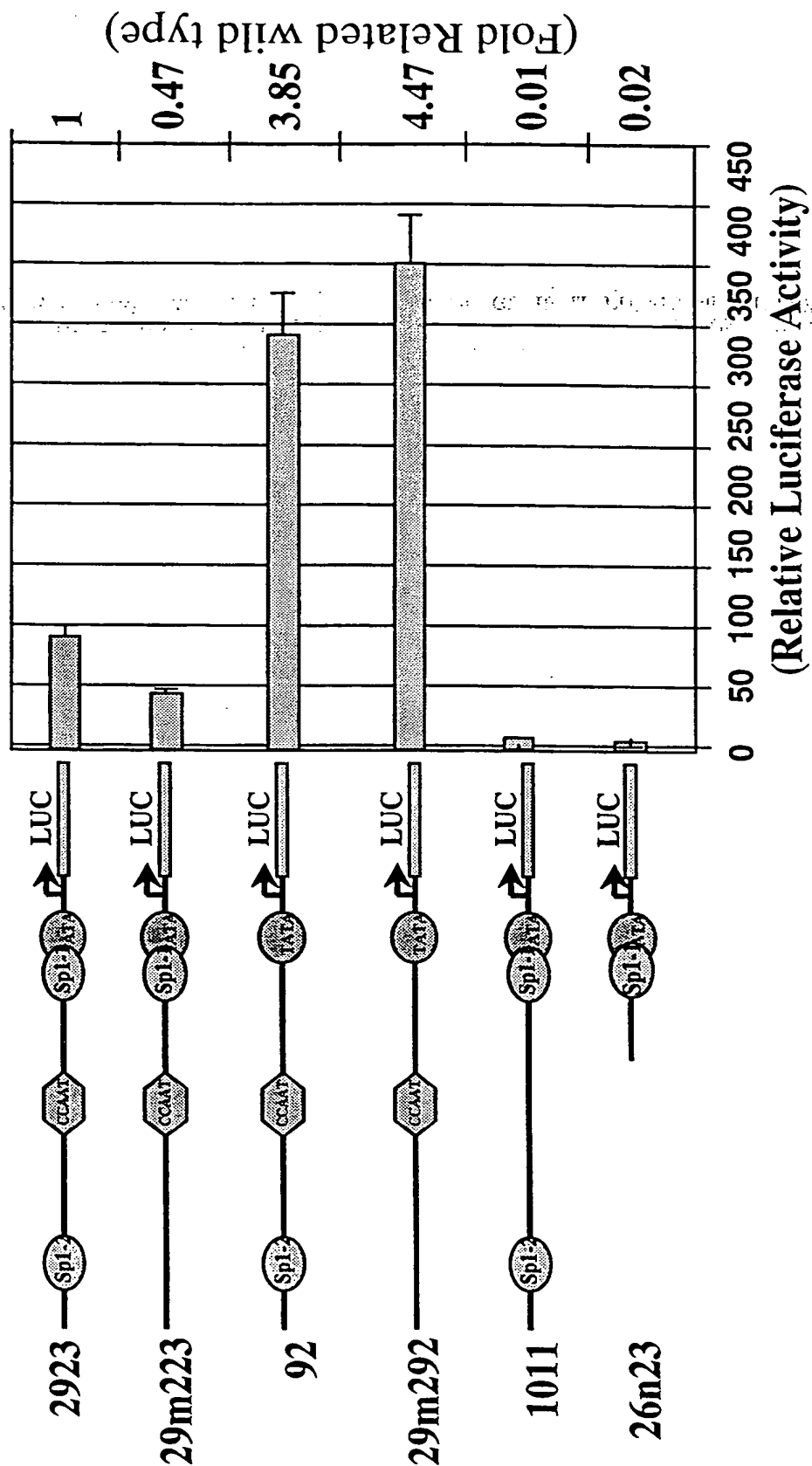


Fig. 21

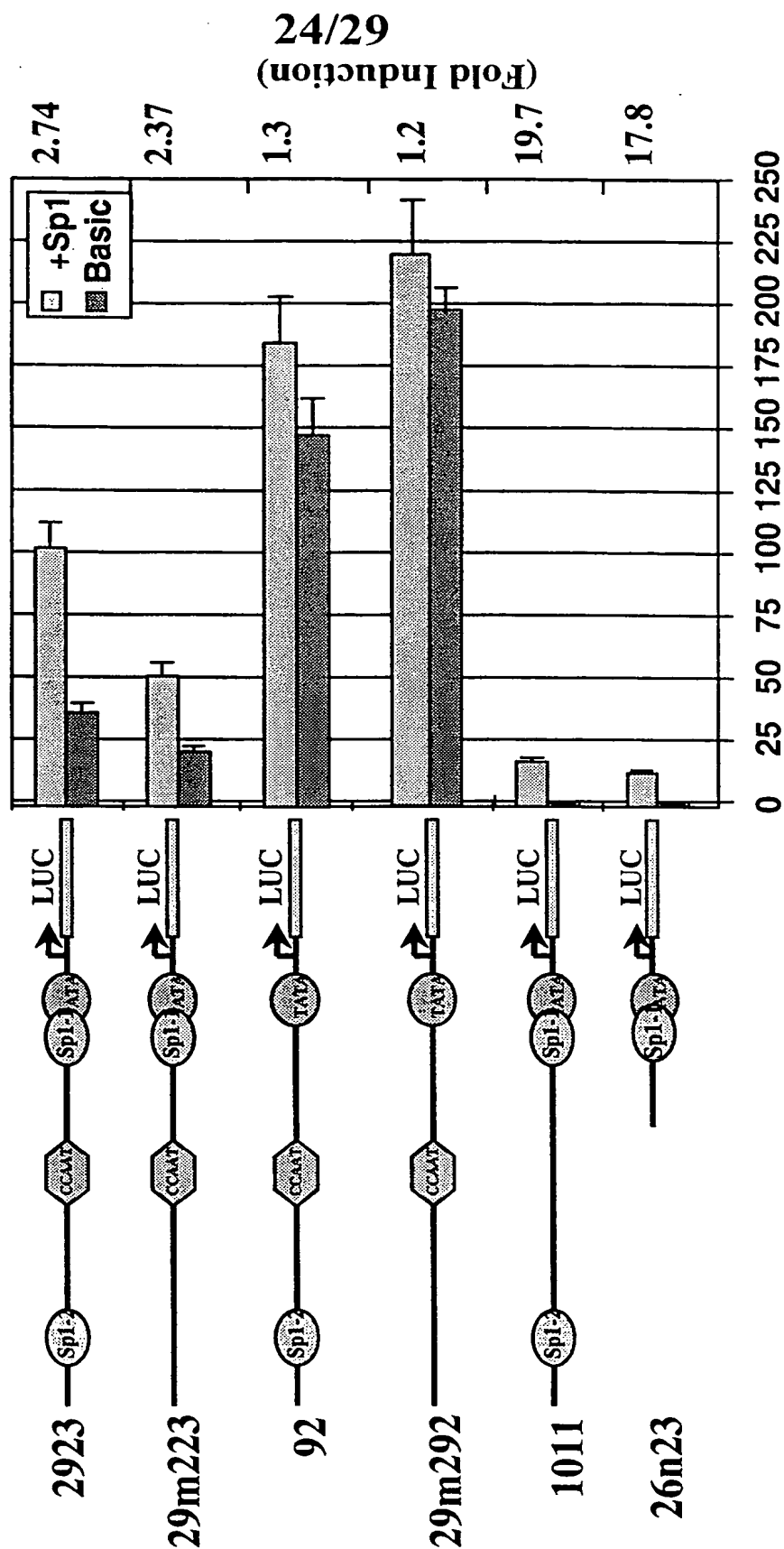


Fig. 22

25/29

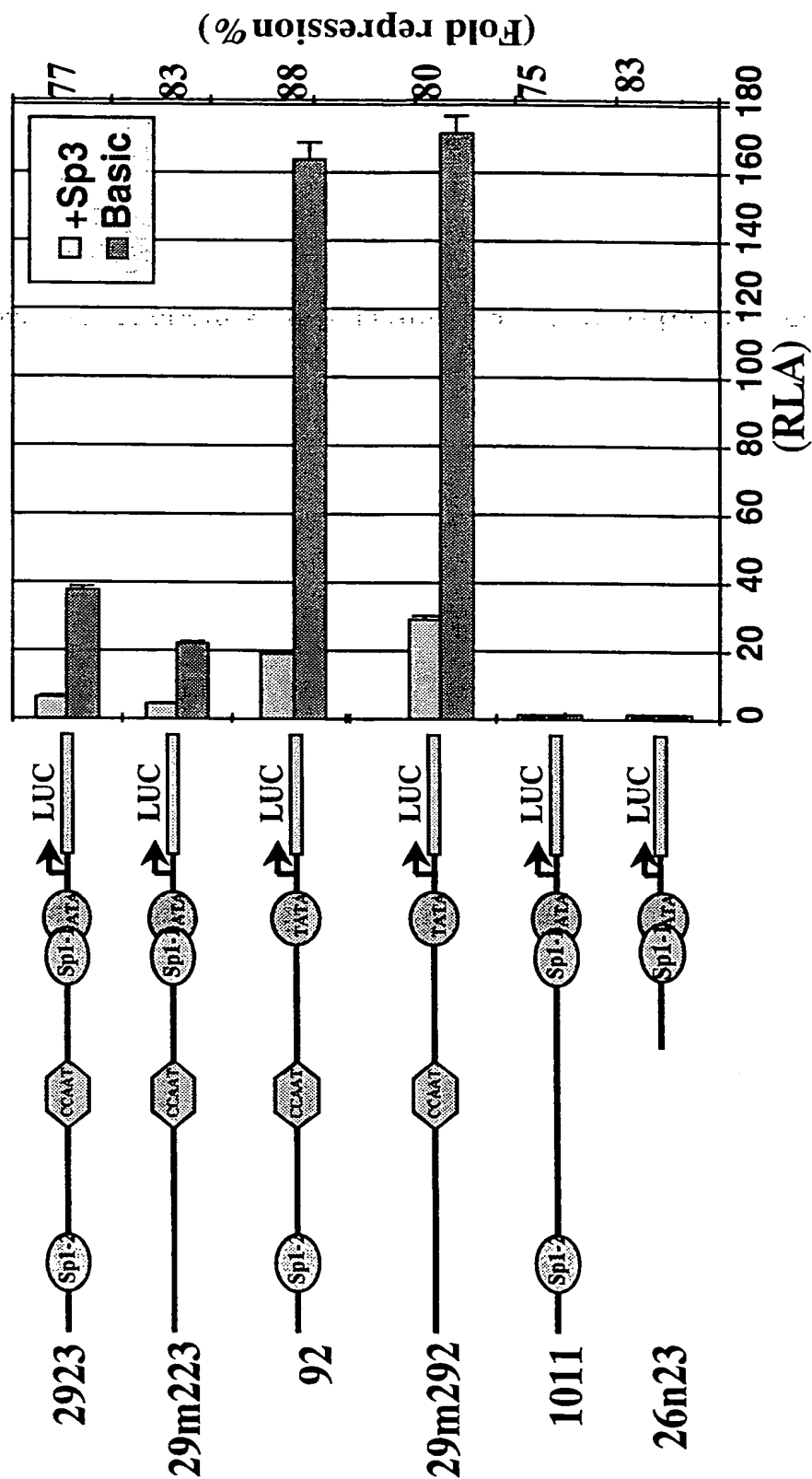


Fig. 23

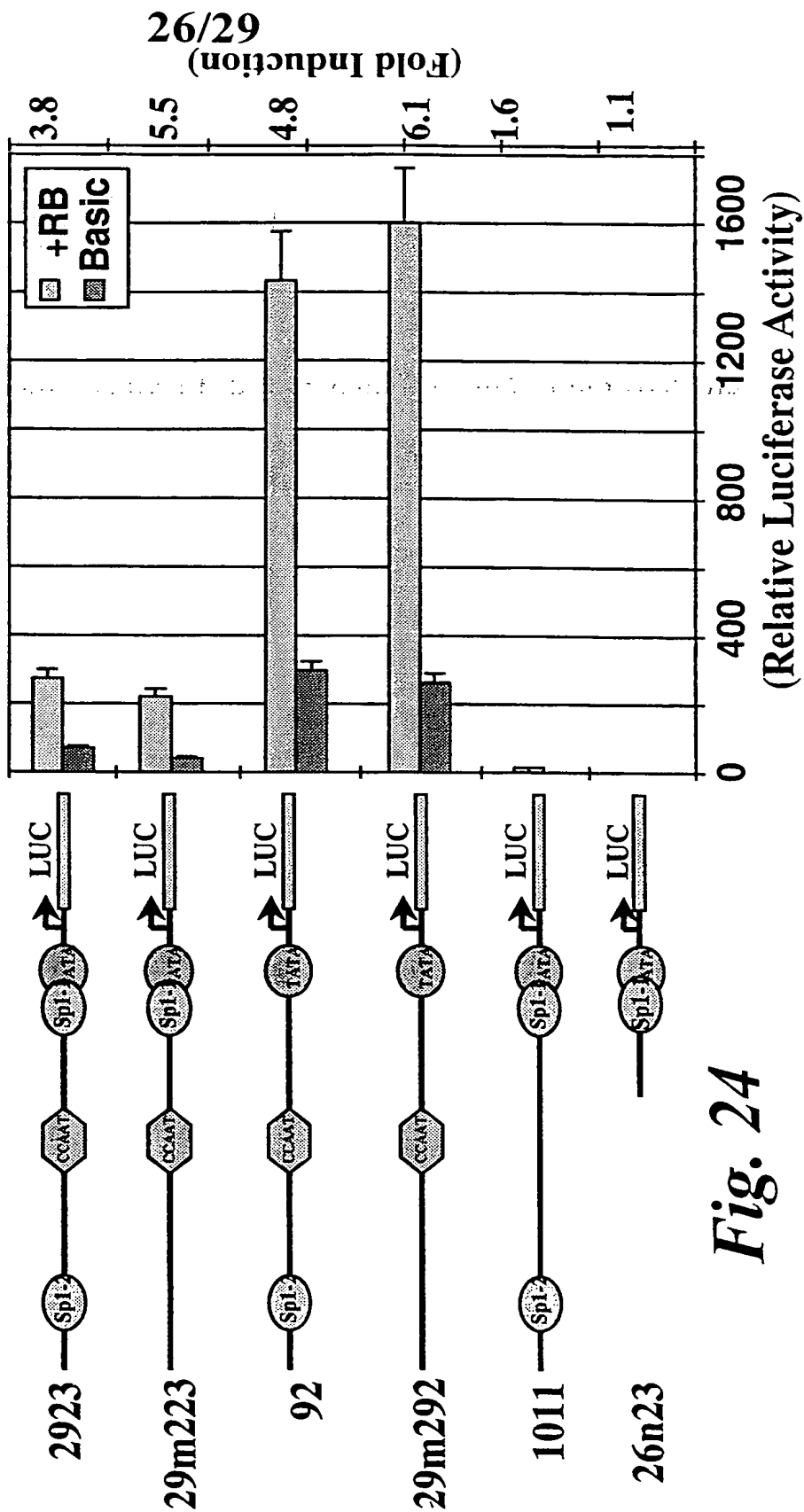
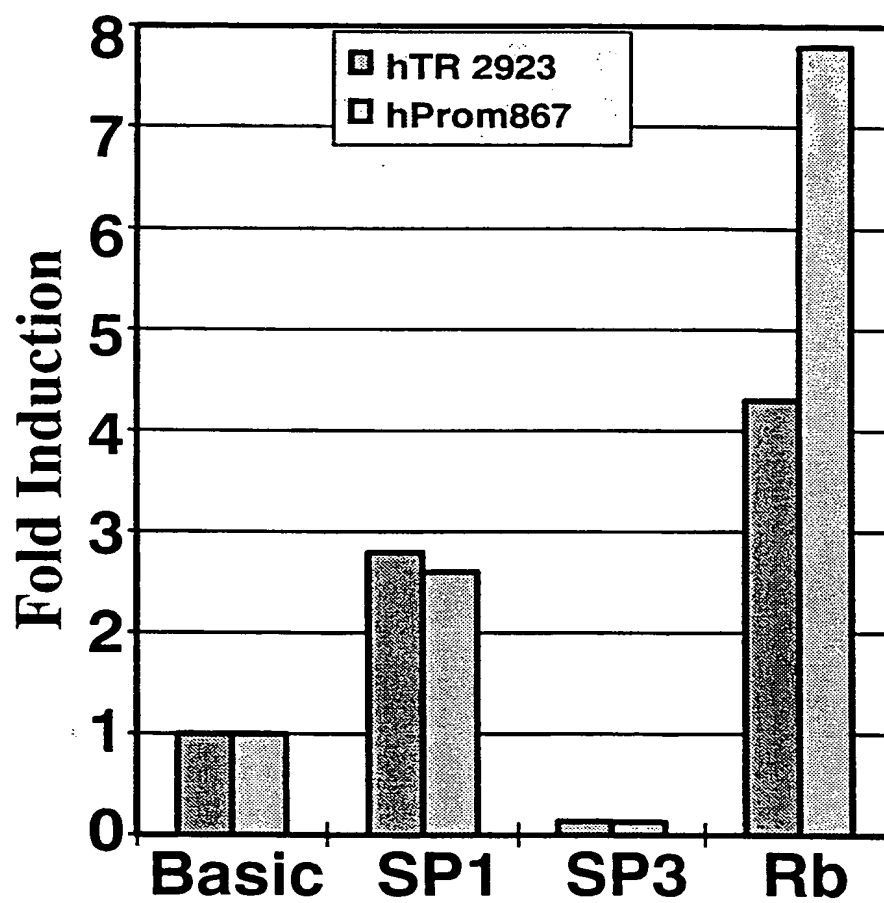


Fig. 24

27/29

*Fig. 25*

28/29

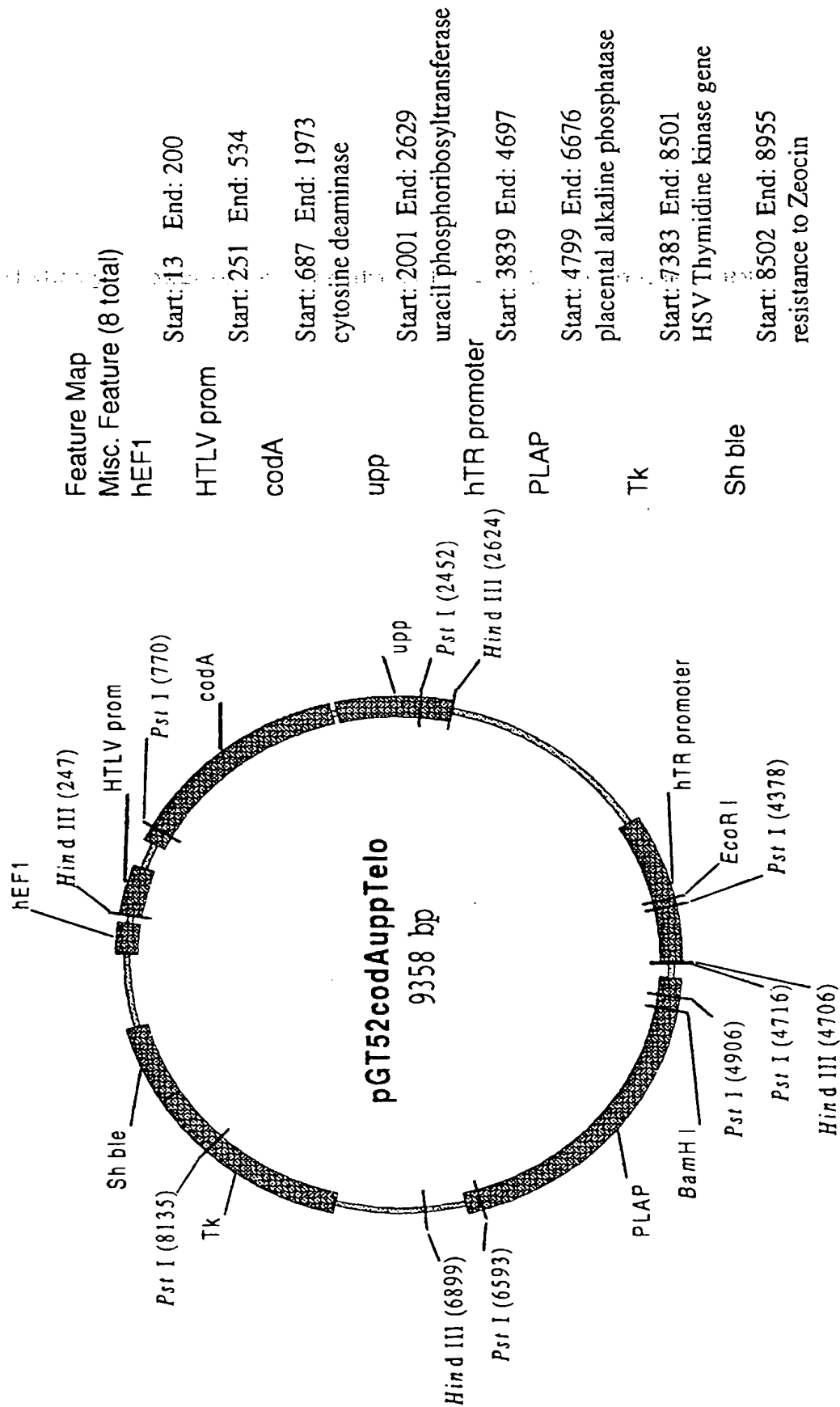


Fig. 26

29/29

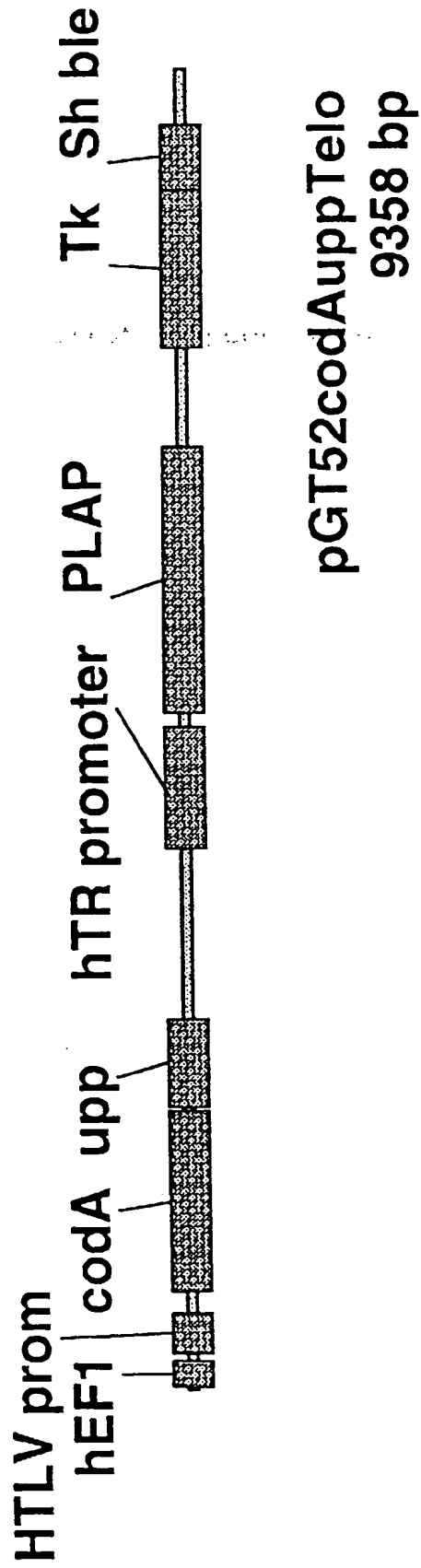


Fig. 27



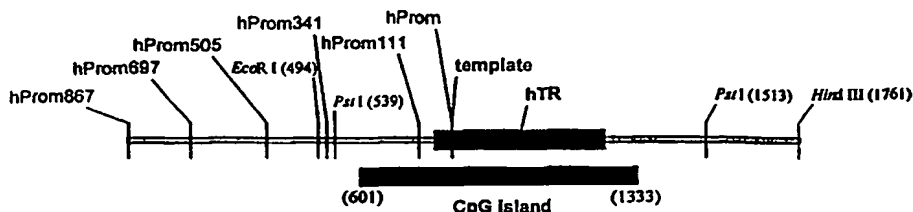
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C12N 15/11, 9/12, 15/85, C12Q 1/68		A3	(11) International Publication Number: WO 99/38964
			(43) International Publication Date: 5 August 1999 (05.08.99)
(21) International Application Number: PCT/GB99/00308		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 29 January 1999 (29.01.99)			
(30) Priority Data: 9801902.9 29 January 1998 (29.01.98) GB			
(71) Applicant (for all designated States except US): CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED [GB/GB]; Cambridge House, 6-10 Cambridge Terrace, Regent's Park, London NW1 4JL (GB).			
(72) Inventor; and (75) Inventor/Applicant (for US only): KEITH, William, Nicol [GB/GB]; CRC Dept. of Medical Oncology, University of Glasgow, CRC Beatson Laboratories, Garscube Estate, Switchback Road, Glasgow G61 1BD (GB).		Published With international search report.	
(74) Agents: CRIPPS, Joanna, E. et al.; Mewburn Ellis, York House, 23 Kingsway, London WC2B 6HP (GB).		(88) Date of publication of the international search report: 20 January 2000 (20.01.00)	

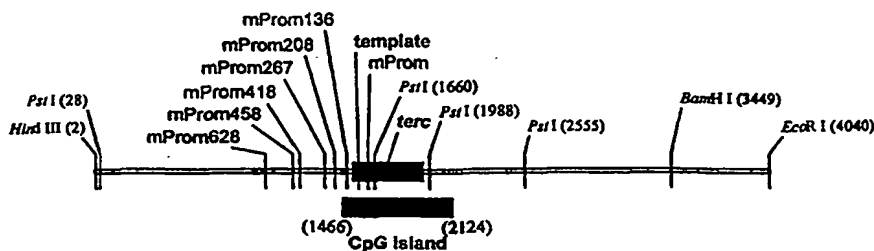
(54) Title: PROMOTER REGIONS OF THE MOUSE AND HUMAN TELOMERASE RNA COMPONENT GENES

(57) Abstract

The present invention relates to the identification of the genomic promoter region of the human and mouse telomerase RNA gene. Telomerase activity is necessary for the unrestricted proliferative capacity of many human cancers. It is proposed that mutation or dysregulation of the telomerase repression pathway may cause reactivation or upregulation of telomerase expression in cancer. The invention provides details of elements important for the regulation of telomerase RNA genes, including the Sp family of transcription factors. There is further provided methods for screening for elements having the ability for suppressing telomerase RNA gene promoter activity and use of such elements in the treatment of cancers. In addition, evidence is also provided for the development of new transcription based therapies for cancer and for genetic approaches to targeting therapeutic genes to cancer cells. Namely, (1) transcriptional repression and the disruption of signal transduction pathways regulating telomerase activation. (2) Tumour specific gene expression for genetic therapy via telomerase RNA gene promoters.



A



B

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

National Application No

PCT/GB 99/00308

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/11 C12N9/12 C12N15/85 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 01835 A (ANDREWS WILLIAM H ;VILLEPONTEAU BRYANT (US); FUNK WALTER (US); FEN) 25 January 1996 (1996-01-25)	1-7, 14, 15, 17, 18, 23-28, 35, 37, 38
Y	page 24, line 13 -page 31, line 19 page 37, line 16 -page 43, line 13	15-21, 26-28, 30, 31, 35, 39-45
A	page 47, line 15 -page 55, line 19 page 65, line 9 -page 66, line 14 --- -/--	26-38

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

5 October 1999

Date of mailing of the international search report

19.10.1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Andres, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/00308

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PALMITER R D ET AL: "CELL LINEAGE ABLATION IN TRANSGENIC MICE BY CELL-SPECIFIC EXPRESSION OF A TOXIN GENE" CELL, vol. 50, 31 July 1987 (1987-07-31), pages 435-443, XP002055685 ISSN: 0092-8674 the whole document	15-21
Y	FENG J ET AL: "THE RNA COMPONENT OF HUMAN TELOMERASE" SCIENCE, vol. 269, no. 5228, 1 September 1995 (1995-09-01), pages 1236-1241, XP000645335 ISSN: 0036-8075 cited in the application	26-28, 30, 31, 35
A	the whole document	1-7
Y	RING, C. ET AL.: "Suicide gene expression induced in tumour cells transduced with recombinant adenoviral, retroviral and plasmid vectors containing the ERBB2 promoter" GENE THERAPY., vol. 3, 1996, pages 1094-1103, XP002117436 ISSN: 0969-7128 the whole document	39-45
X	WO 96 01614 A (ANDREWS WILLIAM H ;VILLEPONTEAU BRYANT (US); FUNK WALTER (US); GRE) 25 January 1996 (1996-01-25) cited in the application page 12, line 28 -page 13, line 25 figures 1,3 example 7	1-8, 14, 17, 18
X	HINKLEY, C. ET AL.: "The mouse telomerase RNA 5'-end lies just upstream of the telomerase template sequence" NUCLEIC ACIDS RESEARCH., vol. 26, 15 January 1998 (1998-01-15), pages 532-536, XP002106807 OXFORD UNIVERSITY PRESS, SURREY., GB ISSN: 0305-1048 the whole document	1-3, 8, 9, 14, 17, 18
X	PARKINSON E K ET AL: "The genetic basis of human keratinocyte immortalisation in squamous cell carcinoma development: the role of telomerase reactivation." EUROPEAN JOURNAL OF CANCER, (1997 APR) 33 (5) 727-34, XP002117437	26, 31, 32, 34, 36-38
A	page 731, paragraph 2 -page 732	26-38
	-/--	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/00308

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>LANDBERG, G. ET AL.: "Telomerase activity is associated with cell cycle deregulation in human breast cancer" CANCER RESEARCH., vol. 57, 1 February 1997 (1997-02-01), pages 549-554, XP002117438 ISSN: 0008-5472</p> <p>---</p>	26-38
A	<p>HART L R : "TISSUE- SPECIFIC PROMOTERS IN TARGETING SYSTEMICALLY DELIVERED GENE-THERAPY" SEMINARS IN ONCOLOGY, (FEB 1996) VOL. 23, NO. 1, PP. 154-158., XP002117439 the whole document</p> <p>---</p>	39-45
A	<p>WO 95 06486 A (OLDFIELD EDWARD J ;RAM ZVI (US); US HEALTH (US); BLAESE R MICHAEL) 9 March 1995 (1995-03-09) page 14, last paragraph -page 15, line 6 example 1 claims</p> <p>---</p>	39-45
A	<p>HARLEY, C. & SHERWOOD, S.: "Telomerase, checkpoints and cancer" CANCER SURVEYS, vol. 29, 1997, pages 263-284, XP002117440</p> <p>---</p>	
A	<p>GREIDER C W: "TELOMERE LENGTH REGULATION" ANNUAL REVIEW OF BIOCHEMISTRY, vol. 65, 1996, pages 337-365, XP002056801</p> <p>---</p>	
P,X	<p>ZHAO, J.-Q. ET AL.: "Cloning and characterization of human and mouse telomerase RNA gene promoter sequences." ONCOGENE, vol. 16, 1998, pages 1345-1350, XP002106808 ISSN: 0950-9232 the whole document</p> <p>---</p>	1-15, 17, 18
P,X	<p>WO 98 11207 A (VILLEPONTEAU BRYANT ;HARLEY CALVIN (US); GERON CORP (US)) 19 March 1998 (1998-03-19) page 23, line 25 -page 32, line 13 page 33, line 27 -page 38</p> <p>-----</p>	1-7, 15, 17-26, 30-32, 34-38

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/00308

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 44 and 45 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,
no additional fees are to be refunded.

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☒ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 99/00308

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 26, 27 and 32 relate to a substance defined by reference to a desirable characteristic or property, namely its ability to modulate the activity of a TR promoter.

The claims cover all substances having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such substances. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the substance by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the specific modulators as defined in claims 28, 29 and 33.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 99/00308

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 2-7 (all totally) and claims 1,14,17-18, 37-38 (all partially)

A nucleic acid comprising a promoter region of the human telomerase RNA gene, constructs, vectors and host cells containing it.

2. Claims: 8-13 (all totally) and claims 1,14,17-18, 37-38 (all partially)

A nucleic acid comprising a promoter region of the mouse telomerase RNA gene, constructs, vectors and host cells containing it.

3. Claims: 16 (totally) and claims 15,17-22 (all partially)

A nucleic acid construct comprising a telomerase RNA gene promoter linked to a cytotoxin, and its use in the treatment of cancer.

4. Claims: 23-36 (all totally) and claims 15, 17-22 (all partially)

A method for screening for a substance being a modulator of the promoter of a telomerase RNA gene, the substances identified and their use in the treatment of cancer or the activation of telomerase.

5. Claims: 39-45

A system for controlling neoplasia.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/00308

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9601835 A	25-01-1996	US 5583016 A	10-12-1996
		US 5776679 A	07-07-1998
		AU 696702 B	17-09-1998
		AU 2964795 A	09-02-1996
		AU 3095095 A	09-02-1996
		AU 9712998 A	18-03-1999
		BG 101103 A	31-10-1997
		BR 9508254 A	23-12-1997
		CA 2194393 A	25-01-1996
		CN 1158617 A	03-09-1997
		CN 1168696 A	24-12-1997
		CZ 9700034 A	15-10-1997
		EP 0778842 A	18-06-1997
		EP 0793719 A	10-09-1997
		FI 970026 A	03-03-1997
		HU 78054 A	28-07-1999
		JP 10505488 T	02-06-1998
		JP 10507067 T	14-07-1998
		NO 970041 A	06-03-1997
		NZ 289720 A	29-03-1999
		PL 318169 A	26-05-1997
		WO 9601614 A	25-01-1998
		US 5876979 A	02-03-1999
		US 5837857 A	17-11-1998
WO 9601614 A	25-01-1996	US 5583016 A	10-12-1996
		US 5876979 A	02-03-1999
		AU 696702 B	17-09-1998
		AU 2964795 A	09-02-1996
		AU 3095095 A	09-02-1996
		AU 9712998 A	18-03-1999
		BG 101103 A	31-10-1997
		BR 9508254 A	23-12-1997
		CA 2194393 A	25-01-1996
		CN 1158617 A	03-09-1997
		CN 1168696 A	24-12-1997
		CZ 9700034 A	15-10-1997
		EP 0778842 A	18-06-1997
		EP 0793719 A	10-09-1997
		FI 970026 A	03-03-1997
		HU 78054 A	28-07-1999
		JP 10505488 T	02-06-1998
		JP 10507067 T	14-07-1998
		NO 970041 A	06-03-1997
		NZ 289720 A	29-03-1999
		PL 318169 A	26-05-1997
		WO 9601835 A	25-01-1996
		US 5776679 A	07-07-1999
		US 5837857 A	17-11-1998
WO 9506486 A	09-03-1995	CA 2169557 A	09-03-1995
		EP 0716614 A	19-06-1996
		JP 9505557 T	03-06-1997
WO 9811207 A	19-03-1998	AU 4351997 A	02-04-1998

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☒ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.